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ANALYSIS OF THE POTENTIAL FOR RADIOFREQUENCY RADIATION BIOEFFECTS TO RESULT FROM OPERATION OF THE PROPOSED ONR AND AIR FORCE HIGH-FREQUENCY ACTIVE AURORAL RESEARCH PROGRAM IONOSPHERIC RESEARCH INSTRUMENT (HAARP IRI): GENERAL ANALYSIS.

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This report has been reviewed and is approved for publication.

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13. ABSTRACT (Maximum 200 words)

"RFR" is an acronym for radiofrequency radiation, which refers to the emission and propagation of electromagnetic waves in the frequency range nominally from 3 kHz to 300 GHz. Such waves are characterized as nonionizing radiation because the intrinsic (quantum) electromagnetic energy absorbed by a body at any frequency within this range is much too low to ionize (eject electrons) from molecules of the body.

Equivalent terms in the literature on RFR bioeffects include electromagnetic radiation (EMR), nonionizing radiation (NIR), nonionizing radiofrequency electromagnetic (RFEM) fields, and electromagnetic fields (EMF). It should be noted, however, that the acronym "EMF" has lately become associated primarily with possible bioeffects of 50-Hz and 60-Hz electric and magnetic fields from powerlines.

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HAARP: HUMAN HEALTH EFFECTS OF RADIOFREQUENCY RADIATION

1. INTRODUCTION

"RFR" is an acronym for radiofrequency radiation, which refers to the emission and propagation of electromagnetic waves in the frequency range nominally from 3 kHz to 300 GHz. Such waves are characterized as nonionizing radiation because the intrinsic (quantum) electromagnetic energy absorbed by a body at any frequency within this range is much too low to ionize (eject electrons) from molecules of the body.

Equivalent terms found in the literature on RFR bioeffects include electromagnetic radiation (EMR), nonionizing radiation (NIR), nonionizing electromagnetic radiation (NIEMR), microwave radiation, microwave fields, radiofrequency electromagnetic (RFEM) fields, and electromagnetic fields (EMF). It should be noted, however, that the acronym "EMF" has lately become associated primarily with possible bioeffects of 50-Hz and 60-Hz electric and magnetic fields from powerlines.

1.1 LITERATURE SELECTION

This document on bioeffects of RFR and their relationship to human health contains analyses of a selection of research papers from the many thousands of accounts in the literature published in scientific journals through about 1991. The papers discussed are grouped under a set of RFR-bioeffects topics; the selection was made to provide representative coverage of each topic. Endeavors were made to describe differences in findings of the papers within each topic, and where possible, to assess the quality of the research. Most of the papers selected were presumed to have undergone peer review before publication. With a few exceptions, presentations at scientific symposia or abstracts thereof were excluded from consideration under the assumption that either more complete and peer-reviewed accounts of such studies will appear subsequently or not at all (perhaps because the study was flawed or the investigators were not able to reproduce their results).

Some of the analyses and critiques herein of papers published before 1987 were derived from a general review document entitled: "Critique of the Literature on Bioeffects of Radiofrequency Radiation: A Comprehensive Review Pertinent to Air Force Operations" (Heynick, 1987), prepared by SRI International under the sponsorship of the U.S. Air Force.

Other general reviews of the literature on RFR bioeffects published from time to time have been studied, among them a report from the EPA by Elder and Cahill (1984), which was to serve as the primary reference for the issuance of an RFR-exposure standard for the general population in the U.S. by the EPA. However, the conclusions in the present document regarding possible effects of exposure of people to RFR were reached independently.

1.2 ASSESSMENT OF SCIENTIFIC INFORMATION AND RISK

Concerned people frequently ask whether guarantees can be given that chronic exposure to low levels of RFR will have no deleterious effects on

people many years in the future. In general, scientists believe that if an experiment done many times shows no effects, then repeating it still more times will most likely also show no effect. However, they have no way of fully guaranteeing that conclusion because to be completely sure about the absence of an effect of any agent would require experiments to assess the effects of that agent be performed an infinite number of times on a large number of different biological systems and endpoints, all with findings of no deleterious effects, clearly an impossible task.

Instead, subject to practical considerations, experiments are done one or more times with specific numbers of subjects and stated conditions or assumptions regarding the agent(s) being investigated, and conclusions about the experiments are based on the use of appropriate statistical treatments of the data. The findings, including those indicative of no effects (negative results) related to the agent(s) studied, are usually given in probabilistic terms (confidence levels) because the data may contain varying degrees of uncertainty related to the accuracy of the instrumentation used and/or uncontrolled variations in the populations and/or levels of the agents investigated.

It must also be recognized that the experimental evidence for any specific RFR bioeffect is derived primarily from the use of laboratory animals as surrogates for humans, a practice widely used in seeking or assessing possible effects of other agents. Thus, most projections about possible effects of RFR on humans are based on findings with species that have much different anatomies and functional characteristics than humans, and which were investigated with RFR and exposure durations that may have differed considerably from those of any specific system.

Some investigations of human exposure to RFR have been done, either with volunteers or as epidemiologic studies. For ethical reasons, very few of the former have been conducted. On the other hand, epidemiologic studies elucidate the distribution of death or disease, often involving large human populations, and describe the probable factors that influence the distribution. However, for RFR as a possible factor, the values of the exposure parameters (especially the intensity levels and durations) vary widely with time for each individual and are highly variable from person to person. Moreover, in the absence of reliable information on exposure, the people included in the "exposed" group are often selected by their occupation, a dubious method, or else it is difficult to find a suitable control group that matches a better defined exposed group in all important aspects except RFR exposure. Nevertheless, positive results of well designed and conducted epidemiologic studies can point to the need for more specific research.

For other agents, possible effects at very low levels are predicted by extrapolating findings at higher levels on the basis of assumptions about the mathematical relationship between the level (or dose) of the agent and the degree of the effect. The existence or nonexistence of thresholds for deleterious effects of various agents has been debated at length. As a practical scientific matter, thresholds do exist at least for some substances, because many natural substances are essential to life at low concentrations and are toxic at higher concentrations.

For RFR, such predictions by extrapolation from high to low levels are open to challenge. Many studies have yielded results showing that low-level exposures to RFR are not cumulative. In effect, the RFR energy that is continually absorbed at low incident power densities is readily dissipated and does not accumulate in the body. Those findings indicate that specific threshold levels must be exceeded to cause various RFR bioeffects. In a few studies, repetitive exposures within about 1 hour of one another at levels just below the thresholds for single-exposure effects were reported to be cumulative, but those levels were relatively high (SARs above 4 W/kg). By contrast, ingestion of certain chemicals in small quantities over time can accumulate in the body into potentially harmful total doses. As will be evident in subsequent sections of this document, there is much experimental evidence to affirm that chronic exposure to RFR at appropriately indicated low levels is not harmful to humans.

1.3 RFR SAFETY STANDARDS

Terms such as "safety standards" and "exposure standards" generally refer to, and are frequently used interchangeably with, specifications or guidelines on maximum exposure levels to electromagnetic fields of the general public or occupationally. Such levels are usually expressed as permissible exposure limits (PELs), threshold limit values (TLVs), or maximum power densities or field intensities in specific frequency ranges for stated exposure durations.

Guidelines for human exposure to RFR have been selected on the basis of maximum values of "specific absorption rate" (SAR) that were found to be not harmful in experimental animal studies. SAR is the rate at which RFR energy is absorbed in any small region of a body, and is expressed in watts per kilogram (W/kg). For any value of incident power density, the SAR usually varies with location of the region within the body. Internal variations of SAR are difficult to determine for complex bodies, so the term "whole-body SAR" is often used to represent the spatially averaged value of SAR for the body, a quantity that can be measured without the need for determining internal variations of local SAR.

In 1982, American National Standards Institute (ANSI) Subcommittee C95.IV had adopted a frequency-dependent standard (ANSI, 1982) for both occupational and general-public exposure to RFR. It covered the frequency range from 300 kHz to 100 GHz. Its maximum allowable exposure limits, displayed in Table A.1, were based on a maximum whole-body SAR of 4 W/kg reduced by a safety factor of 10, or 0.4 W/kg. Those limits were not to be exceeded for exposures averaged over any 6-minute period. The lowest incident power density limit was 1 mW/cm^2 for the subrange 30-300 MHz in which RFR absorption by the human body as a resonant entity is highest.

TABLE A.1: ANSI (1982) RADIOFREQUENCY RADIATION PROTECTION GUIDES

(1) Frequency Range (MHz)	(2) E^2 (V^2/m^2)	(3) H^2 (A^2/m^2)	(4) Power Density (mW/cm^2)
0.3 - 3	400,000	2.5	100
3 - 30	$4{,}000x(900/f^2)$	$0.025x(900/f^2)$	$900/f^2$
30 - 300	4,000	0.025	1.0
300 - 1,500	4,000x(f/300)	0.025x(f/300)	f/300
1,500 - 100,000	20,000	0.125	5.0

Note: f is the frequency in MHz.

In the far field of an RFR source, the governing maxima are the power densities shown in column 4 of Table A.1, and the corresponding squares of the electric-field and magnetic-field amplitudes (E^2 and H^2) in columns 2 and 3 are the approximate "free-space" equivalents, defined as follows for 1 mW/cm^2 (10 W/m^2):

$$E^2 = (Z_0) \times 10\ W/m^2 \qquad (A.1)$$

$$H^2 = (1/Z_0) \times 10\ W/m^2, \qquad (A.2)$$

where Z_0 represents the impedance or value of E/H for free space, but rounded up from 377 to 400 ohms to yield limit values to one significant figure only.

In the near field of an RFR source, the governing maxima are the values of E^2 and H^2. In such exposure situations, the values of E^2 and H^2 can be expressed in terms of corresponding power densities by using equations A.1 and A.2, but primarily for convenience in expressing the entire standard in terms of a single parameter (power density).

The 1982 ANSI standard has the following exclusions:

(1) At frequencies between 300 kHz and 100 GHz, the protection guides may be exceeded if the exposure conditions can be shown to produce SARs below 0.4 W/kg as averaged over the whole body and spatial peak values below 8 W/kg as averaged over any one gram of tissue.

(2) At frequencies between 300 kHz and 1 GHz, the protection guides may be exceeded if the RF input power of the radiating device is 7 W or less. [This exclusion was provided in recognition that many low-power devices in common use by the general population may produce fields that appear to exceed the exposure guides in local regions of the body close to the devices but which would yield whole-body SARs much lower than those in the exposure guides.]

The American Conference of Governmental Industrial Hygienists published threshold limit values (ACGIH, 1984) also based on 0.4 W/kg but intended for occupational exposures only. These TLVs, to be averaged over any six-minute period, are shown in Table A.2. Later ACGIH publications on this subject contained no revisions to these TLVs.

TABLE A.2: ACGIH (1984) RADIOFREQUENCY/MICROWAVE THRESHOLD LIMIT VALUES

Frequency Range (MHz)	Power Density (mW/cm^2)	E^2 (V^2/m^2)	H^2 (A^2/m^2)
0.01-3	100	377000	2.65
3-30	$900/f^2$	$3770x(900/f^2)$	$900/(37.7xf^2)$
30-100	1	3770	0.027
100-1000	f/100	3770xf/100	f/(37.7x100)
1000-300,000	10	37700	0.265

One major difference between the 1982 ANSI and 1984 ACGIH standards was that the 1-mW/cm^2 value in the latter extends only from 30 to 100 MHz and rises with a slope f/100 at 100 MHz to 10 mW/cm^2 at 1 GHz. This difference is based on the premise that children, who have higher whole-body resonant frequencies than adults (see Section 2.1), are not likely to be occupationally exposed to RFR. Also different in the 1984 ACGIH standard is that the equivalent free-space field intensities for 1 mW/cm^2 are given by equations 1 and 2 but with Z0 = 377 ohms instead of the rounded up value 400 ohms. Last, the lower frequency limit for the 100-mW/cm^2 TLV of the ACGIH standard is at 10 kHz instead of 300 kHz. On the basis of whole-body SAR, this TLV appears to be safe, but does not exclude possible occurrence of RF shocks or burns under some conditions. The 1984 ACGIH standard provides procedures for minimizing such possible hazards. The TLVs are intended for use in the practice of industrial hygiene only by persons trained in that discipline.

The currently applicable permissible exposure limits (PELs) for the Air Force are given in the Air Force Occupational Safety and Health Standard 161-9 (AFOSH, 1984). These PELs are shown in Table A.3:

TABLE A.3: AFOSH (1984) MAXIMUM PERMISSIBLE LIMITS FOR EXPOSURE TO RFR (AVERAGED OVER ANY SIX-MINUTE PERIOD)

Frequency Range (MHz)	PEL for Average-Size Adult (mW/cm^2)	PEL for Small-Size Human (mW/cm^2)
0.01-3	100	100
3-30	$900/f^2$	$900/f^2$
30-100	1	1
100-300	f/100	1
300-1000	f/100	f/300
1000-1500	10	f/300
1500-300,000	10	5

The following notes pertain to Table A.3:

(1) All exposures must be limited to a maximum (peak) electric field intensity of 100 kV/m.

(2) f is the frequency in MHz.

(3) Use the PELs under the heading "Average Size Adult" for Air Force workers and workplaces. Use the more restrictive PELs under the heading "Small Size Human" when assessing potential hazards in areas where the public has unrestricted access.

(4) A small size human is an individual less than 55 inches (140 cm) tall.

(5) When exposure is to multiple-frequency radiation, the sum of the fractions of the PELs at the separate frequencies must not exceed unity.

(6) When an RF emitter operates over a band of frequencies in which the PEL varies, such as between 3 and 30 MHz, the lowest PEL shall apply.

In a report by Scientific Committee 53 of the National Council on Radiation Protection and Measurements (NCRP, 1986), the 1982 ANSI limits were recommended for occupational exposure only. Recommended for the general population were exposure limits based on 0.08 W/kg, a fivefold lower value than in the 1982 ANSI guidelines. The corresponding lowest power-density limit in the NCRP report is 0.2 mW/cm^2, applicable to the frequency range 30 to 300 MHz. This reduction was based on the assumption that the general public is exposed continuously (168 hours per week) and that the ratio of 40 hours in the work week to 168 hours is about 0.2.

In 1988, the functions of ANSI Subcommittee C95.IV were transferred to Subcommittee IV of Standards Coordinating Committee (SCC) 28, a new body under jurisdiction of the Institute of Electrical and Electronics Engineers (IEEE). The Subcommittee selected and analyzed the important research papers in an updated data base of the RFR-bioeffects literature, and prepared a revision of the 1982 ANSI guidelines. That revision (SCC 28, 1991) was approved by the IEEE and will be published shortly.

The SCC 28 (1991) guidelines cover the frequency range from 3 kHz to 300 GHz and separately specify the maximum allowable RFR exposures in "uncontrolled environments" (accessible by the general population) and "controlled environments" (such as occupational exposure). The guidelines for uncontrolled environments are displayed in Table A.4 and graphically in Figure A.1. Those for controlled environments are shown in Table A.5 and graphically in Figure A.2. The averaging times are given in minutes.

TABLE A.4: SCC 28 (1991) MAXIMUM PERMISSIBLE EXPOSURE LIMITS FOR UNCONTROLLED ENVIRONMENTS*

Frequency Range (MHz)	E (V/m)	H (A/m)	Power Density,S (mW/cm^2)	Averaging Time $0E0^2$,S	$0H0^2$
0.003 - 0.1	614	163	**	6	6
0.1 - 1.34	614	16.3/f	**	6	6
1.34 - 3.0	823.8/f	16.3/f	**	$f^2/0.3$	6
3.0 - 30	823.8/f	16.3/f	**	30	6
30 -100	27.5	$158.3/f^{1.668}$	**	30	0.0636f
100 - 300	27.5	0.0729	0.2	30	30
300 - 3000			f/1500	30	
3000 - 15000			f/1500	90000/f	
15000 - 300000			10	$616000/f^{1.2}$	

TABLE A.5: SCC 28 (1991) MAXIMUM PERMISSIBLE EXPOSURE LIMITS FOR CONTROLLED ENVIRONMENTS*

Frequency Range (MHz)	E (V/m)	H (A/m)	Power Density,S (mW/cm^2)	Averaging Time $0E0^2$,$0H0^2$, or S
0.003 - 0.1	614	163	**	6
0.1 - 1.34	614	16.3/f	**	6
1.34 - 3.0	823.8/f	16.3/f	**	6
3.0 - 30	823.8/f	16.3/f	**	6
30 -100	27.5	$158.3/f^{1.668}$	**	6
100 - 300	27.5	0.0729	0.2	6
300 - 3000			f/1500	6
3000 - 15000			f/1500	6
15000 - 300000			10	$616000/f^{1.2}$

The following notes pertain to both of the SCC 28 tables above:

*The exposure values in terms of electric and magnetic field strengths are the values obtained by spatially averaging values over an area equivalent to the vertical cross section of the human body (projected area).

**The equivalent plane-wave power densities for these frequency ranges can be calculated by using equations A.1 and A.2, with Z_0 = 377 ohms. Although such calculated power densities are not appropriate for near-field conditions, they are useful for comparison with the higher frequency ranges.

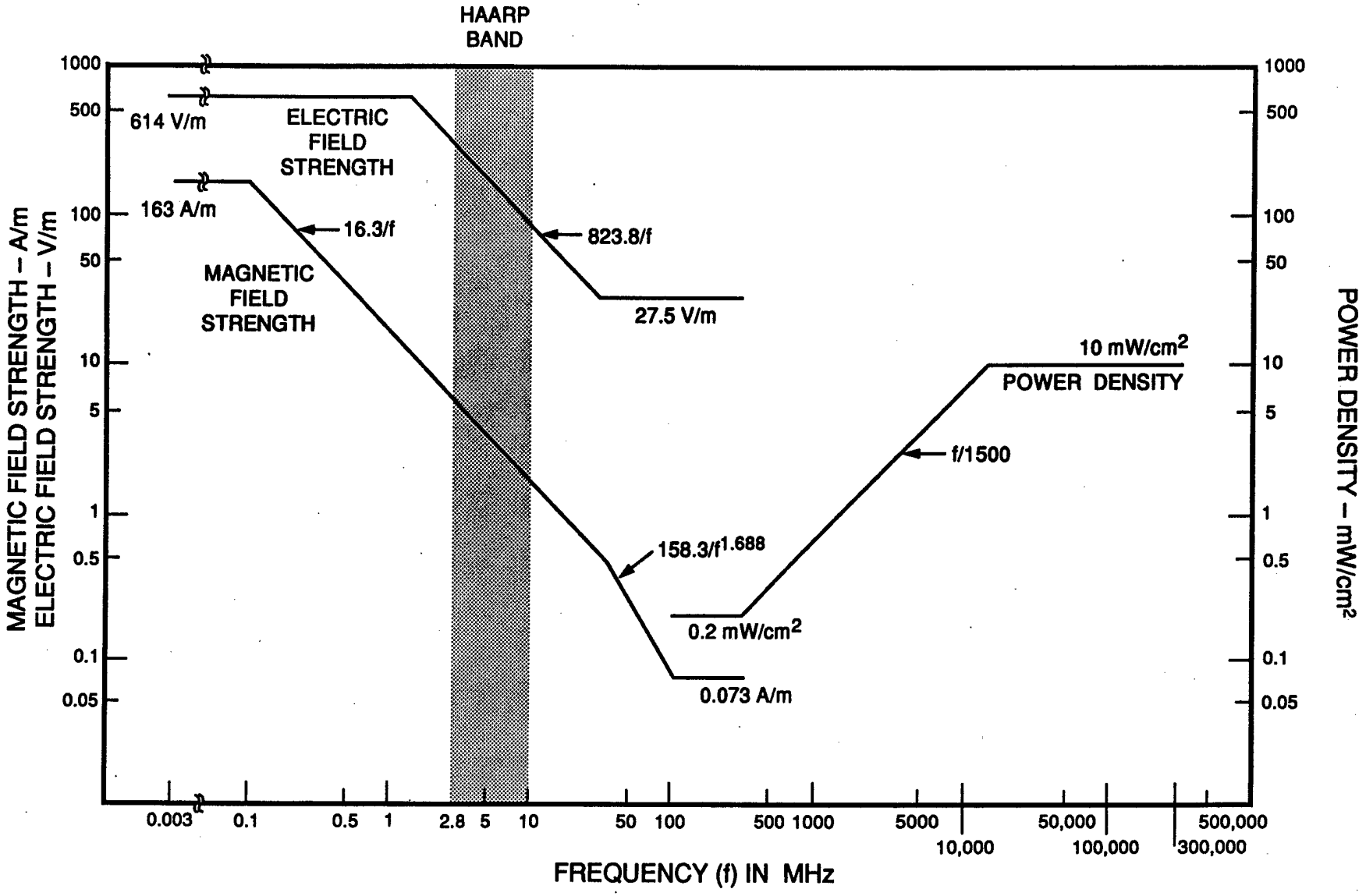

FIGURE A.1 Maximum Permissible Exposure for Uncontrolled Environments

Source: IEEE SCC 28 (1991)

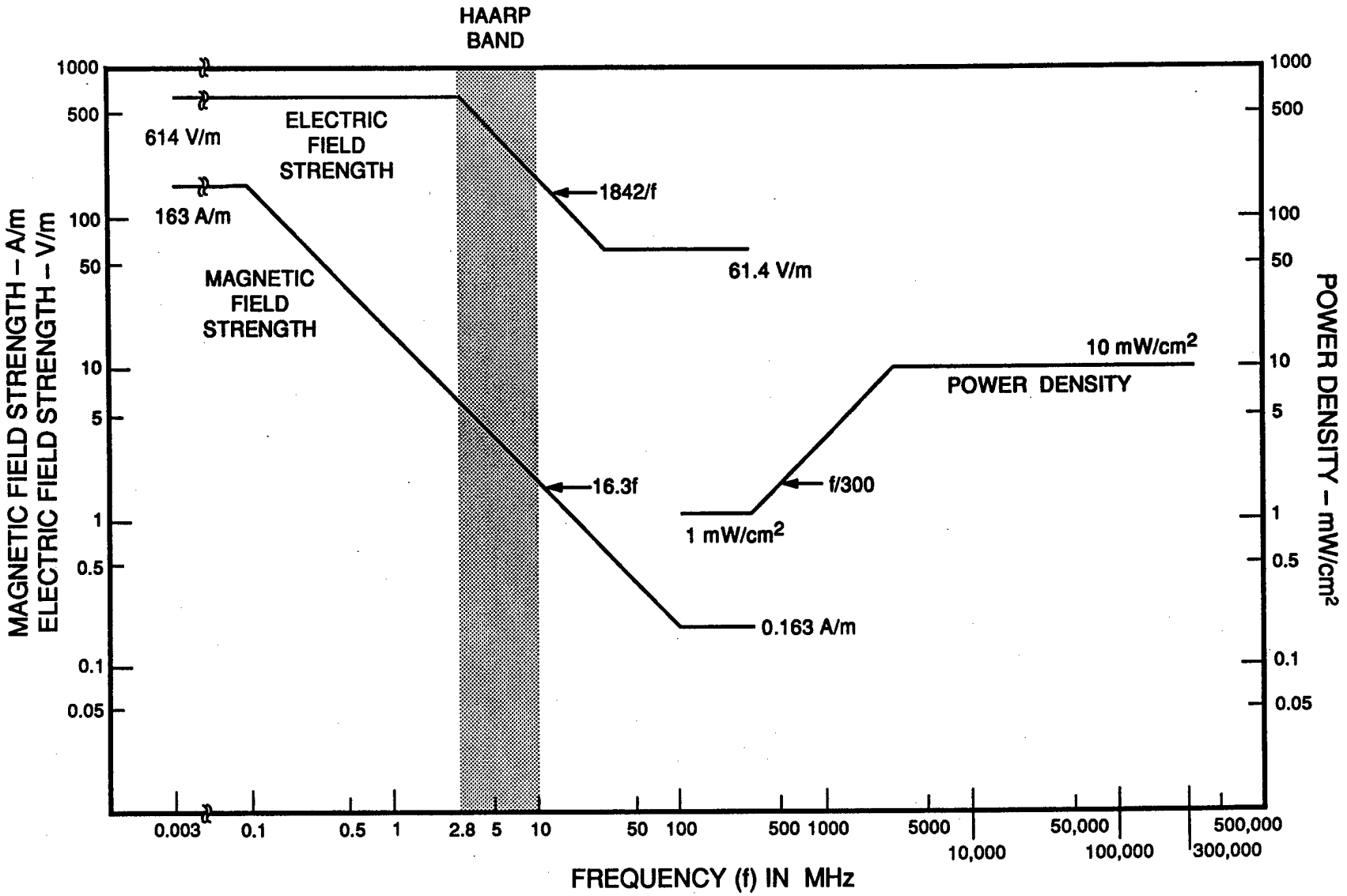

FIGURE A.2 Maximum Permissible Exposure for Controlled Environments

Source: IEEE SCC 28 (1991)

Also included in the SCC 28 (1991) guidelines are maximum allowable values of radiofrequency current flow induced within the feet of a person immersed in an RFR field or by the person's contact with an inanimate object (such as a fence or vehicle) electrically charged by immersion in an RFR field. The limits for uncontrolled and controlled environments, shown respectively in Tables A.6 and A7, are applicable only within the frequency range from 3 kHz to 100 MHz (where such effects can occur).

TABLE A.6: SCC 28 (1991) LIMITS ON INDUCED AND CONTACT CURRENTS UNCONTROLLED ENVIRONMENTS

Frequency Range (MHz)	Maximum Current (mA)		
	Through both feet	Through each foot	Contact
0.003 - 0.1	900f	450f	450f
0.1 - 100	90	45	45

TABLE A.7: SCC 28 (1991) LIMITS ON INDUCED AND CONTACT CURRENTS CONTROLLED ENVIRONMENTS

Frequency Range (MHz)	Maximum Current (mA)		
	Through both feet	Through each foot	Contact
0.003 - 0.1	2000f	1000f	1000f
0.1 - 100	200	100	100

For several years, the Environmental Protection Agency (EPA) had been planning to issue an exposure standard for the general population. The previously mentioned review by Elder and Cahill (1984) was to have served as the basis for such a standard, but none was issued.

In the absence of a governing Federal standard (but not necessarily for that reason), various state, county, and municipal bodies have issued ordinances on exposure of the general population to RFR that are usually more stringent than those of ANSI (1982) or SCC 28 (1991). Most such standards refer to the 4 W/kg SAR used as the basis of the 1982 ANSI guidelines, but with a safety reduction factor of 50 [to 0.08 W/kg] instead of 10.

Regarding exposure guidelines in other countries, the International Non-Ionizing Radiation Committee of the International Radiation Protection Association, with participants from Australia, France, Federal Republic of Germany, Italy, the Netherlands, Sweden, the U.K., and the U.S., published guidelines (IRPA, 1988) for occupational and general-public exposure to RFR in the frequency range 0.1-300 GHz. The occupational exposure limits in the range 10 MHz upward were based on a whole-body SAR of 0.4 W/kg, and are fivefold lower (based on 0.08 W/kg) for the general public. Those limits are displayed in Table A.8. Environmental health criteria issued by the World Health Organization (WHO, 1981) served as the rationale.

TABLE A.8: IRPA/INIRC (1988) MAXIMUM PERMISSIBLE LIMITS FOR OCCUPATIONAL EXPOSURE TO RFR (AVERAGED OVER ANY SIX-MINUTE PERIOD)

Frequency f (MHz)	E (V/m)	H (A/m)	P_{eq} (W/m^2)	P_{eq} (mW/cm^2)
0.1-1	614	1.6/f	--	--
>1-10	614/f	1.6/f	--	--
>10-400	61	0.16	10	1
>400-2000	30f	0.0080f	f/40	f/400
>2000-300 000	137	0.36	50	5

For part-body exposure in the range 10 MHz upward, the maximum SARs are 20 W/kg in the extremities (hands, wrists, feet, and ankles) and 10 W/kg in any other part of the body.

The limits for exposure of the general public, shown in Table A.9, are based on a whole-body SAR of 0.08 W/kg (a fifth of the occupational SAR), and are also to be averaged over any 6-minute period.

TABLE A.9: IRPA/INIRC (1988) MAXIMUM PERMISSIBLE LIMITS FOR GENERAL PUBLIC EXPOSURE TO RFR (AVERAGED OVER ANY SIX-MINUTE PERIOD)

Frequency f (MHz)	E (V/m)	H (A/m)	P_{eq} (W/m^2)	P_{eq} (mW/cm^2)
0.1-1	87	0.23/0f	--	--
>1-10	87/0f	0.23/0f	--	--
>10-400	27.5	0.073	2	0.2
>400-2000	1.3750f	0.00370f	f/200	f/2000
>2000-300 000	61	0.16	10	1

The IRPA/INIRC guidelines also specify a maximum body-to-ground current of 200 mA and suggested limits on pulsed RFR per se. Regarding shocks and burns, the guidelines state: "Hazards of RF burns should be eliminated by limiting currents from contact with metal objects. In most situations this may be achieved by reducing the E values from 614 to 194 V/m in the range from 0.1 to 1 MHz and from 614/f to 194/0f in the range from >1 to 10 MHz...In general, RF burns will not occur from currents on point contact of 50 mA or less." About pulsed RFR, the guidelines suggest that the pulse power density (averaged over the pulse duration) not exceed 1000 times the specified average plane wave power density limits, or that the peak field strengths not exceed 32 times the specified field strengths.

Of interest are the exposure standards of the U.S.S.R. (Czerski, 1985) before its recent transformation into a confederation of independent republics. For frequencies below 300 MHz, the exposure limits (ELs) are given separately for the E-field and H-field. For the range 300 MHz to 300 GHz, the concept "permissible energy load" or allowable product of incident power density and exposure duration (PT) is used in the occupational standard,

subject to a maximum power density of 1 mW/cm^2. The 1984 occupational ELs and PTs are shown in Table A.10.

TABLE A.10: U.S.S.R. OCCUPATIONAL STANDARD FOR EXPOSURE TO RFR (1984)

Frequency (MHz)	E-Field EL (V/m)	H-Field EL (A/m)
0.06-1.5	50	5
1.5-3	50	*
3-30	20	*
30-50	10	0.3
50-300	5	*
300-300000	**	*

*No EL specification for H-field in this frequency range.
**PT = 2 $W.hr/m^2$ for stationary fields; PT = 20 $W.hr/m^2$ for rotating or scanning antennas (beams).

The 1984 U.S.S.R. ELs for the general population in the frequency range 30 kHz to 300 MHz are shown in Table A.11. No H-field ELs are specified. For the frequency range 300 MHz to 300 GHz, the limit is on power density, 0.1 W/m^2 (0.01 mW/cm^2).

TABLE A.11: U.S.S.R. STANDARD FOR PUBLIC EXPOSURE TO RFR (1984)

Frequency (MHz)	E-Field EL (V/m)
0.03-0.3	25
0.3-3	15
3-30	10
30-300	3

Presumably, those standards remain in effect during the transition. The more-stringent standards in the U.S.S.R. relative to those of the U.S. reflected basic differences in philosophy in the standard-setting processes of the two countries. In the U.S., small deviations from physiological norms are not necessarily considered clinically significant (thereby recognizing that an effect, though real, may not be a hazard). By contrast, Trakhtenberg in the U.S.S.R. (quoted in Goldmann, 1982) defined significant changes as "characterized by the deviation of the factors studied beyond the limits of annual or seasonal fluctuations by more than two standard deviations away from the norm." In many cases, however, such deviations may not necessarily have medically important implications. It is also noteworthy that the military establishment of the U.S.S.R. has been exempt from its exposure standards, but the U.S. military is not.

1.4 MEASUREMENTS OF ENVIRONMENTAL LEVELS OF RFR IN SELECTED U.S. CITIES AND AT SPECIAL LOCATIONS

The Environmental Protection Agency (EPA) measured the environmental field intensities at selected locations in 15 U.S. cities (Janes et al.,

1977). Although the measurements were done more than a decade ago, they are still of interest because of the low values obtained. Measurement sites in each city were selected to permit analyses and estimations of the cumulative fractions of the total population in each city exposed at or below various average power densities, based on the population figures derived from the 1970 census-enumeration districts. The results for those cities (comprising a total of 486 sites) were presented by Janes (1979) and by Tell and Mantiply (1980). They were also summarized in Hankin (1985) and in EPA (1986).

The measured field strengths at each site were integrated over the frequency bands (54 to 890 MHz) included in the analyses and converted into equivalent average power densities. The site values in each city were then used, with the population figures for the census enumeration districts, in a statistical model designed to estimate the population-weighted median exposure value for that city, and for calculating other statistics of interest.

The population-weighted median value for each city was defined as the average power density at or below which half the population of the city was being exposed. The estimates were based on the assumption that the people were under continuous exposure at their place of residence. The estimates did not endeavor to account for population changes since the 1970 census, population mobility, exposure at heights greater than 6.4 meters (20 ft), attenuation of signals by buildings, or periods of time when any of the contributing RFR sources were not transmitting.

The median exposure values ranged from 0.002 $\mu W/cm^2$ for Chicago and San Francisco to 0.02 $\mu W/cm^2$ for Portland (Oregon). The population-weighted median for all 15 cities was 0.048 $\mu W/cm^2$. Also, the percentages of the population exposed to less than 1 $\mu W/cm^2$ in each city ranged from 97.2% (for Washington, D.C.) to 99.99% (for Houston, Texas), with a mean percentage for all cities of 99.44%. The major contributions to those values were from FM-radio and TV broadcast stations.

EPA had also measured the RFR levels at sites close to single or multiple RFR emitters, e.g., at the bases of transmitter towers and at the upper stories (including the roof) of tall buildings or hospital complexes in the vicinity of transmitter towers. At the base of an FM tower on Mt. Wilson, CA, the fields were found to range from about 1 to 7 mW/cm^2 (Tell and O'Brien, 1977). Most of the measurements in tall buildings near FM and TV transmitters yielded values well below 0.01 mW/cm^2, but a few values were close to or slightly exceeded 0.2 mW/cm^2 (e.g., 0.23 mW/cm^2 on the roof of the Sears Building, Chicago).

More recently, a team of EPA and FCC personnel found considerably higher levels in a few sites close to broadcast towers of AM radio (0.55-1.5 MHz) and FM radio (88-108 MHz) in Hawaii (cited in MICROWAVE NEWS, January/February 1985). Next to a tower in Kaimuki having one FM station and three AM stations, for example, the highest AM magnetic field was about 9 A/m, the square of which is about 32 times higher than the 1982 ANSI standard for the frequency range 0.3-3 MHz. Whether transient or intermittent exposure to such AM-RFR levels would be harmful is subject to debate. In most areas accessible by the general public, the levels were within the 1982 ANSI standard.

2 INTERACTIONS OF RFR WITH BIOLOGICAL ENTITIES

2.1 IONIZING RADIATION VERSUS NON-IONIZING RADIATION

Many people are not aware of the differences between nonionizing radiation (such as RFR) and ionizing radiation, so they are concerned that the well known hazards of exposure to ionizing radiation can also occur from exposure to RFR.

Ionizing radiations, such as ultraviolet light, X-rays, emissions from radioactive materials, gamma and cosmic rays, have frequencies millions and trillions of times higher than those of RFR. A "quantum" of any of those radiations has enough intrinsic energy to ionize (eject an electron from) a molecule. The ejection of an electron from a molecule leaves the molecule positively charged, thereby greatly altering its own properties and enhancing its interactions with its neighboring molecules. The resulting effects can be cumulative and irreversible, and thus can profoundly affect human health. For this reason, devices for monitoring cumulative exposures over time (total doses) of ionizing radiation, such as film badges, are commonly used.

Members of the general public are exposed in varying degrees to naturally occurring forms of ionizing radiation, including ultraviolet light from the sun, radioactive materials in the earth (including those released from mining and burning of coal and the release of radon gas), and gamma and cosmic rays from outer space. Added to those are emissions from human-created equipments such as X-ray machines for various purposes (diagnosis, dentistry) and ultraviolet lamps for sun-tanning.

By contrast, because of their vastly lower frequencies, quanta of nonionizing radiation (such as RFR) have intrinsic energies far too small to ionize molecules within a body, but they can agitate molecules, the equivalent of adding heat to the body. However, absorption of RFR within a body as heat would not be clinically significant unless the incident power density is high enough to add the heat at a rate comparable to or higher than the body's metabolic rate. (Also, no additional molecular agitation is produced when RFR exposure ceases, so the heat induced by sequences of RFR exposures at low levels would not be cumulative.)

The heat induced in a given mammalian species by exposure to RFR at relatively low incident power densities normally can be compensated for by the thermoregulatory capabilities of that species, so if any effects are produced, they are usually reversible. However, depending on the species, the heat produced at relatively high intensities may exceed the thermoregulatory capabilities of that species, so compensation for such effects may be inadequate. Thus, exposure at high intensities could cause thermal distress or even irreversible thermal damage.

The general public is exposed to RFR from many kinds of generators and propagators designed by humans. The most prominent RFR sources are the radio and television broadcast transmitters (both public and private) and the many types of radar and communications systems for various other purposes. It is

also necessary to consider the RFR associated with the use of RFR-generating appliances in the home (and elsewhere) such as microwave ovens.

2.2 EFFECTS VERSUS HAZARDS

An effect produced within a body by RFR exposure may not necessarily be deleterious to that body. As an example of a nonhazardous effect, the absorption of visible light (electromagnetic radiation having intrinsic [quantum] energies above those of RFR but below those of ultraviolet light and the other ionizing radiations mentioned previously) in the eyes is necessary for vision. However, light at high intensities (many quanta per second) may be damaging to the retina. Also, visible and infrared radiation are absorbed by the skin, and at normal levels are converted into harmless heat. However, excessive absorption of ultraviolet light can cause skin cancer.

2.3 THERMAL INTERACTIONS AND SPECIFIC ABSORPTION RATES (SARs)

Consider now the effects of continuous-wave (CW) RFR on a human or an animal. The relative magnetic permeability of most organic substances is about unity. Therefore, thermal interactions of RFR with a biological body are dependent on the complex-dielectric and thermal properties of the body's constituents and their distribution within the body, as well as on the RFR's characteristics (frequency, power density, polarization). In the context of nonthermal interactions, it should be noted that the term "local SAR" denotes the rate of energy absorption at any local site within a biological object, and does not necessarily indicate that such absorption occurs as heat. Rather, it is a useful measure of the local field strength resulting from RFR exposure, especially at internal field strengths too low to produce heat at biologically significant rates.

Because the index of refraction of any material is related to its dielectric constant, RFR is reflected and refracted at boundaries between regions of differing dielectric properties, such as at the air-surface interface of a body, for the same physical reasons as those that apply to light incident at an air-glass interface. This is also true at internal boundaries between constituents having different dielectric properties, thereby affecting the variation of electric field with internal location. Figure A.3 is a graph of the fraction of power transmitted (not reflected) at an air-muscle interface versus RFR frequency. At 3.0 GHz, for example, about 44% of the incident power density enters the body, with the remaining 56% being reflected at the surface.

The fraction of incident power density that enters a body undergoes progressive attenuation with depth because of energy absorption. The term "penetration depth" is usually used to quantify such attenuation. For homogeneous specimens and RFR incidence perpendicular to the surface, penetration depth is defined as the distance at which power density is decreased by absorption to about 14% of its value just within the body's surface. A graph of penetration depth versus frequency for muscle tissue is shown in Figure A.4. At 3.0 GHz, for example, the penetration depth for muscle and other high-water tissues is about 1.7 cm (2/3 of an inch). Not shown in that figure is that at about 30 GHz and higher, penetration is largely confined to the outer layers of the skin (much like for sunlight).

In the RFR-bioeffects literature, the energy absorbed by a body from an incident electromagnetic field is usually quantified by the "specific absorption rate" (SAR). The SAR in a small mass at any location within a body is the rate at which energy is absorbed by the constituents in that mass, expressed in watts per kilogram of mass (W/kg). The local SAR thus defined at any site within a body depends on the characteristics of the incident RFR (carrier frequency, modulation, amplitudes and directions of its components), and on the properties of the body and location of the site. For bodies of complex shape and large internal spatial variations in properties, local SAR values are difficult to determine by experiment or calculation. Instead, the "whole-body SAR," representing the spatial average SAR for the body, is often used because it can be determined without requiring any information on the internal variation of SAR.

Researchers have calculated whole-body SARs for models of relatively simple geometry such as spheroids, ellipsoids, and cylinders that have weights and dimensions approximately representative of various species, including humans. Others have experimentally verified such calculations by exposing physical models in various orientations to linearly-polarized plane-wave RFR and determining distributions of heat produced therein.

An important general result is that for exposure of any given model to linearly-polarized plane-wave RFR, the largest value of whole-body SAR would occur when the longest dimension of that model is parallel to the electric component of the RFR, called the "E" orientation, and when the wavelength of the RFR is about 2.5 times the longest dimension of that model (or conversely, the longest dimension is 0.4 of a wavelength). The adjective "resonant" is used for that wavelength or for its corresponding frequency; at resonance, the model absorbs RFR energy much like a lossy half-wave-dipole. Exposure at other orientations yields lower SARs.

Many of the important results of such theoretical and experimental investigations were embodied in a series of handbooks issued by the U.S. Air Force. The last handbook issued (Durney et al., 1986) summarizes the data in previous editions and contains other pertinent information as well. Of particular interest are the plots of calculated whole-body SAR versus frequency for prolate-spheroidal models of an "average" man, woman, and 5-year-old child for exposure to 1 mW/cm^2 in three orientations (Durney et al., 1986, pp. 6.4, 6.7, 6.9), reproduced as Figures A.5, A.6, and A.7. Analogous plots for a prolate-spheroidal model of a medium rat (p. 6.17) are shown in Figure A.8 for comparison. Those plots all display the aforementioned resonances in the E-orientation, with sharp reductions in SAR below each resonant frequency and slower decreases above the resonant frequency.

Specifically, the resonant frequency for the "average" man, taken to be 5 ft 9 inches tall (1.75 m) and weighing about 154 lb (70 kg), is about 70 MHz (when insulated from ground). At this frequency, the whole-body SAR is about 0.2 W/kg for an incident plane-wave power density of 1 mW/cm^2. This SAR is about 1/6 of his resting metabolic rate or 1/20 to 1/90 of his metabolic rate when doing exercise ranging from walking to sprinting. By calculation,

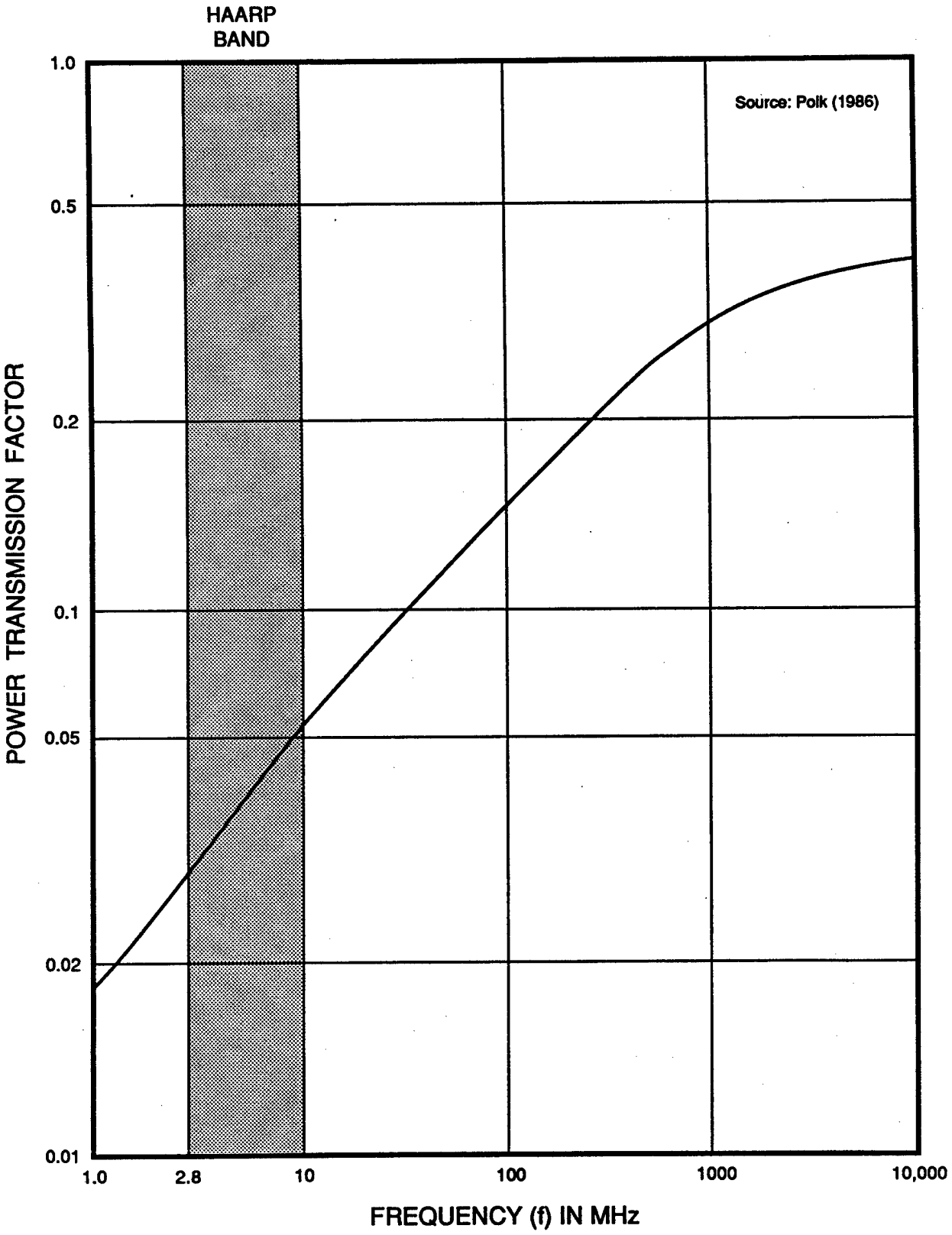

FIGURE A.3 Power Transmission Factor for Air-Muscle Interface, Perpendicular Incidence

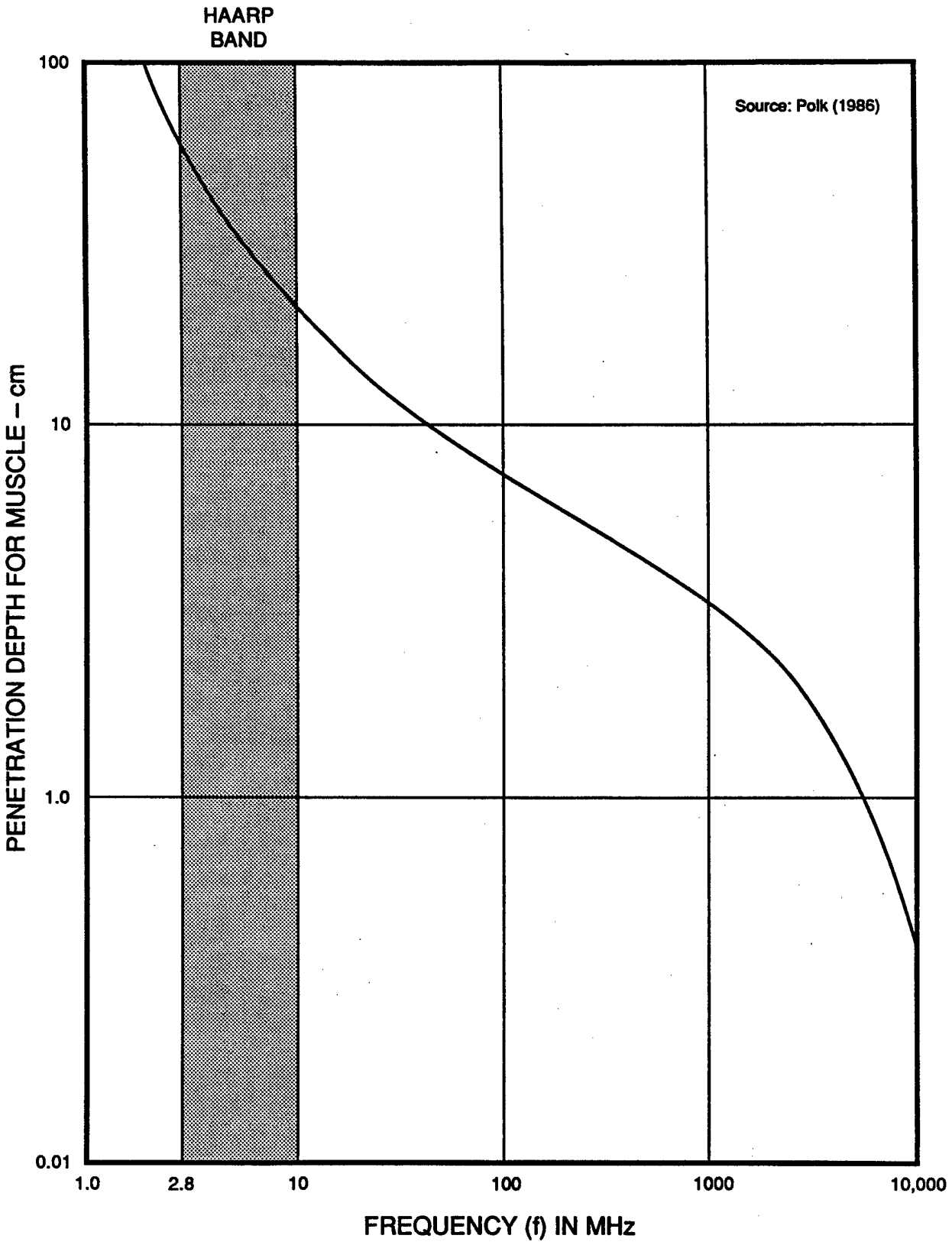

FIGURE A.4 Penetration Depth Versus Frequency for Muscle Tissue

exposure of a man at this SAR (to 1 mW/cm^2) for, say, 1 hour would produce a mean temperature increase of about 0.2 °C with no heat-removal mechanisms (conduction, convection, radiation) operating. Actual temperature increases would be smaller with such heat-exchange mechanisms present. In addition, the compensation exercised by the thermoregulatory systems of live mammals may prevent any rises in body temperature.

Similarly, the resonant frequency for a prolate-spheroidal model of an "average" woman about 5 ft 3 inches tall (insulated from ground), is about 80 MHz, and her mean SAR is about the same as for the average model man. For the model of a 5-year-old child, the resonant frequency is about 110 MHz, and the resonant SAR is about 0.3 W/kg per 1 mW/cm^2.

By contrast, the resonant frequency for a prolate-spheroidal model of a medium rat is about 650 MHz, and the resonant whole-body SAR is about 0.8 W/kg per mW/cm^2. These values and those for other laboratory animals used in RFR-bioeffects studies are important in assessing the results of such animal studies relative to possible effects in humans.

Calculations indicate that if humans were to stand in bare feet on a wet surface, their resonant frequencies would be approximately halved but their whole-body SARs (at the lower resonant frequency) would be higher.

Under some conditions, the SARs of various parts of the body, such as the head and limbs, also require consideration. In an important early study, Shapiro et al. (1971) calculated distributions of fields that would be induced in a multilayered spherical model of a primate head by exposure to 3.0-GHz plane-wave RFR. Their calculations indicated the existence of local internal regions of relatively high fields. Johnson and Guy (1972) obtained experimental results confirming the presence of such regions. Kritikos and Schwan (1975) did similar studies for frequencies in the range from 300 MHz to 12 GHz. In general, the locations of such regions depend on the size of the head, the electromagnetic and thermal properties of its layers, and the frequency of the incident field. Such regions have been dubbed "hot spots," even for combinations of power density and exposure duration that would yield biologically insignificant temperature rises at such spots.

Numerical calculations of internal spatial distributions of SAR have been done for "block" models. In such models, the shape of the body is approximated by an appropriate arrangement of many rectangular cells or blocks of various sizes, with each block assumed biologically homogeneous and to have constant internal field over its volume when the model is exposed to RFR. Also, the biological properties ascribed to each block are selected to approximate those of the tissues in the corresponding location of the body. By spatial averaging over such models, more accurate values of whole-body SAR have been derived than from simpler ones.

Rukspollmuang and Chen (1979), using a block model of an isolated multilayered spherical head, obtained results that were qualitatively similar to those of Kritikos and Schwan (1975). They then studied, at 918 MHz and 2.45 GHz, a block model with shape and internal structure more closely approximating that of the human head (including eyes, nose, skull bone, and

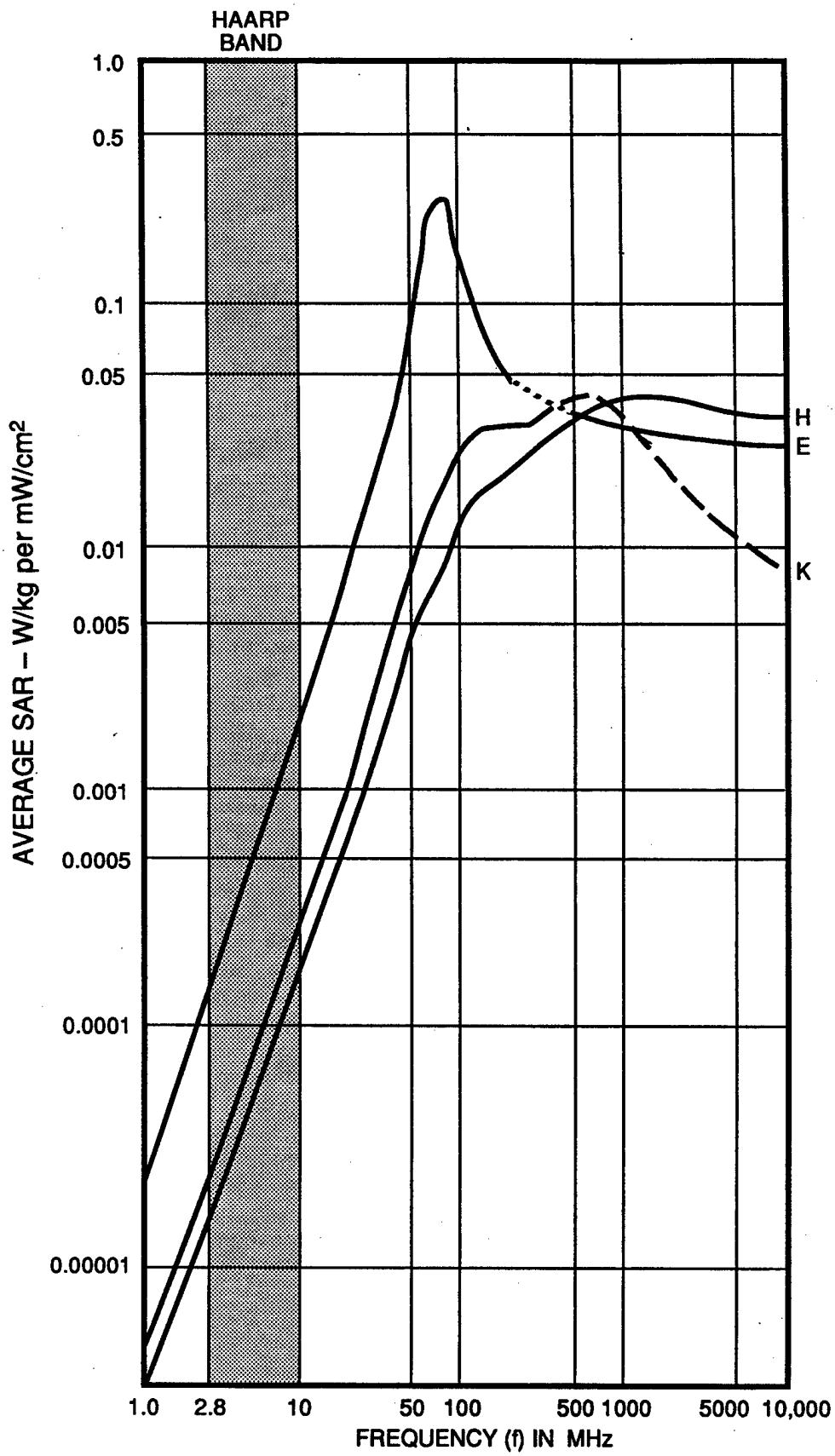

FIGURE A.5 Calculated plane-wave average SAR versus frequency for an average man in the E, H, K orientations. (Prolate spheroidal model, three polarizations; a = 0.875 m, b = 0.138 m, V = 0.07 m^3.)

Source: RFR Dosimetry Handbook, (2nd Ed., 1976), (4th Ed., 1986)

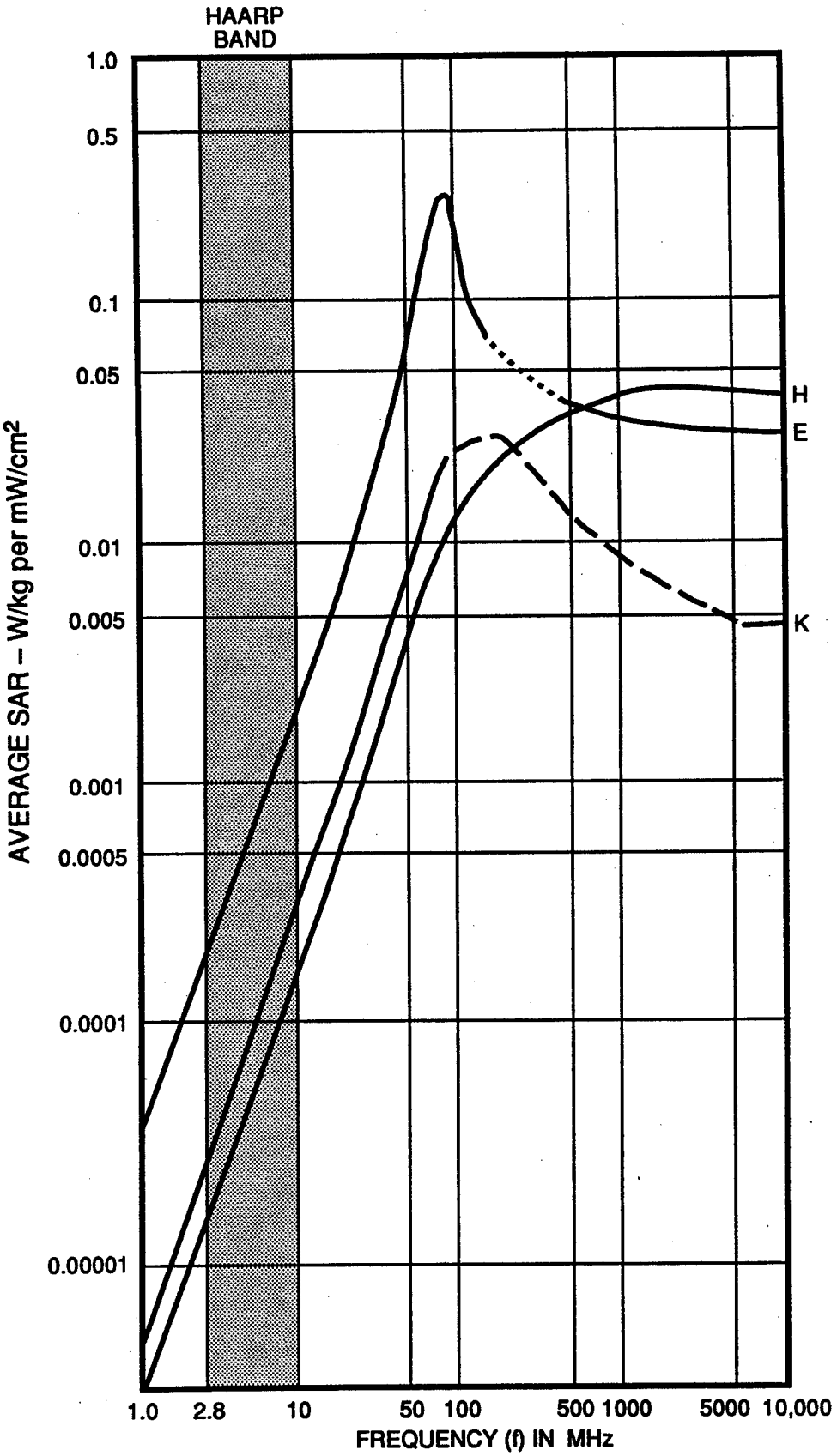

FIGURE A.6 Calculated plane-wave average SAR versus frequency for an average woman in the E, H, K orientations. (Prolate spheroidal model, three polarizations; a = 0.805 m, b = 0.135 m, V = 0.06114 m^3.)

Source: RFR Dosimetry Handbook, (2nd Ed., 1976), (4th Ed., 1986)

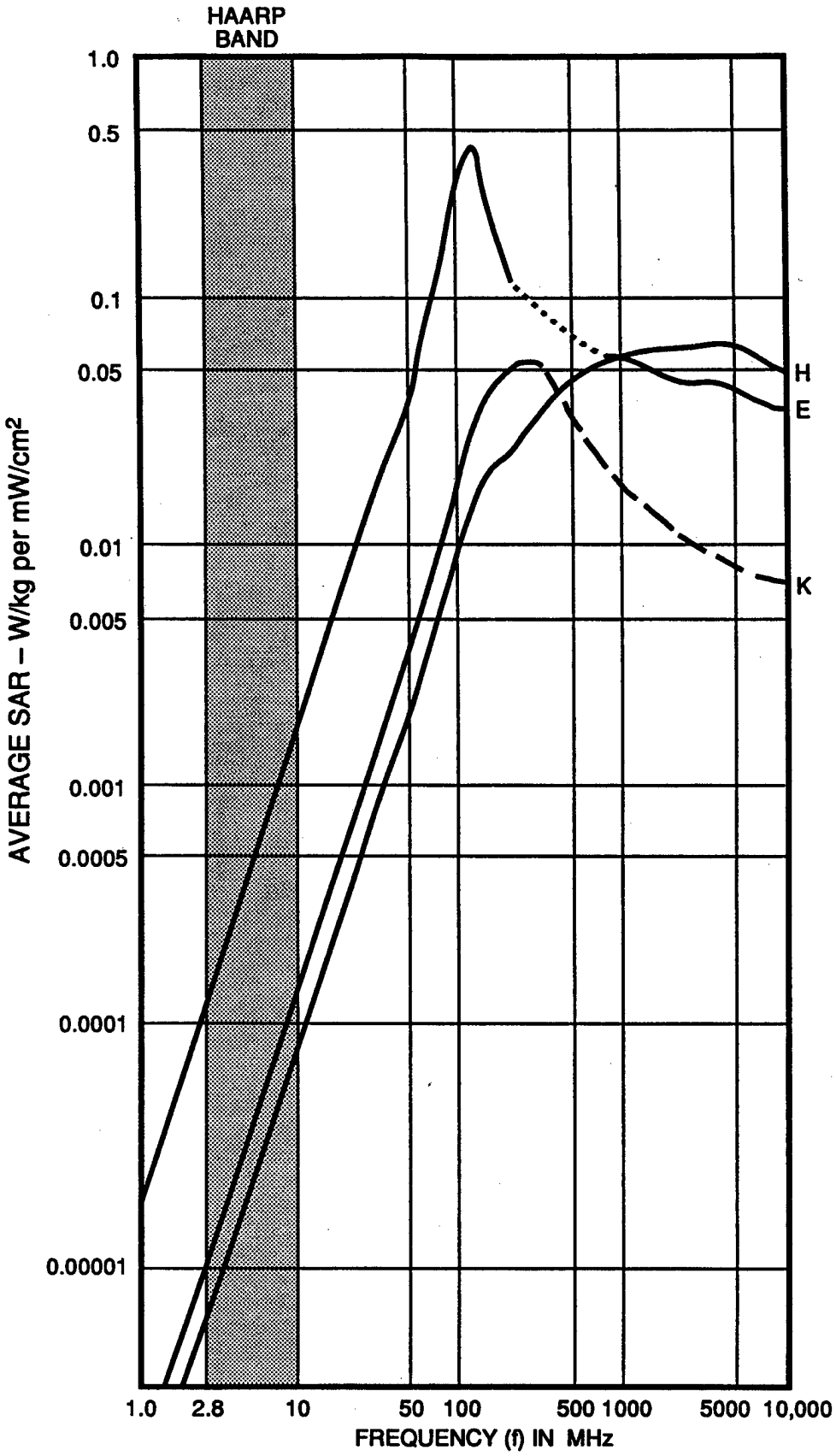

FIGURE A.7 Calculated plane-wave average SAR versus frequency for a prolate spheroidal model of an average 5-year-old child in the E, H, K orientations. (Prolate spheroidal model, three polarizations; a = 0.56 m, b = 0.091 m, V = 0.0195 m^3.)

Source: RFR Dosimetry Handbook, (2nd Ed., 1976), (4th Ed., 1986)

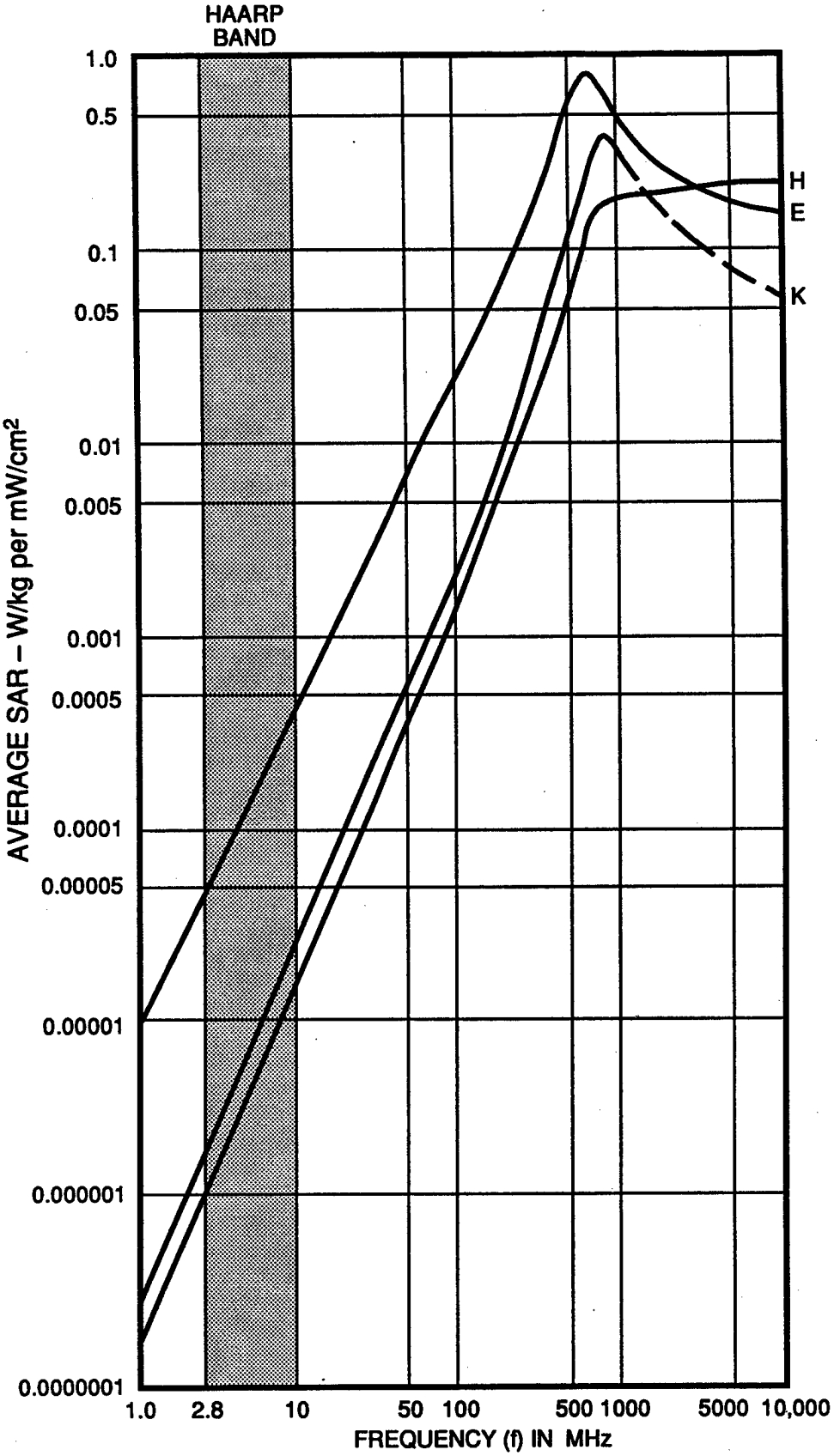

FIGURE A.8 Calculated plane-wave average SAR versus frequency for a medium rat in the E, H, K orientations. (Prolate spheroidal model, three polarizations; a = 0.1 m, b = 0.0276 m, V = 3.2 x 10^{-4} m^3.)

Source: RFR Dosimetry Handbook, (2nd Ed., 1976), (4th Ed., 1986)

brain), and found that much of the energy would be absorbed within the skull. Also, frontal exposure of the model to 2.45 GHz would induce fields that are primarily concentrated near the front surface, and therefore energy dissipation within the brain would be relatively low.

Hagmann et al. (1979) calculated SAR distributions in the attached head of a block model of a human, and derived whole-head and whole-body SARs for three orientations of the model relative to the source of RFR. For front-to-back propagation with the long axis of the body parallel to the electric vector, they found a broad head resonance at about 350 MHz, with a whole-head SAR of about 0.12 W/kg per mW/cm^2; the corresponding whole-body SAR is about 0.05 W/kg per mW/cm^2. For propagation in the head-to-toe direction, a sharper head resonance at 375 MHz was obtained, with whole-head and whole-body SARs respectively approximately 0.22 and 0.07 W/kg per mW/cm^2.

Results of numerical analyses of whole-body SARs and internal SAR distributions were subjected to experimental verification. Figurines of humans and animals constructed from synthetic biological materials having electromagnetic characteristics approximating their various biological constituents were exposed to RFR at power densities sufficient to produce accurately measurable temperature increases. Such temperature rises were determined right after exposure. An important qualitative result is that at frequencies near resonance, local internal fields for human figurines can be much higher for regions such as the neck and groin than for other locations in the body. Also, for nonprimate figurines, the variations of internal field with location are quite different from those for primate figurines, a finding that must be considered in attempting to extrapolate experimental results for laboratory animals to humans, or when comparing experimental results between two (or more) laboratory species.

2.4 NONTHERMAL INTERACTIONS AND SARs

Under similar exposure conditions, the whole-body SARs obtained with amplitude-modulated (AM) RFR at any given carrier frequency and average power density are the same as those of CW RFR or frequency-modulated (FM-CW) RFR. In the context of nonthermal interactions, it should be noted that the term "local SAR" denotes the rate of energy absorption at any local site within a biological object, and does not necessarily indicate that such absorption occurs as heat. Rather, it is a useful measure of the local field strength resulting from RFR exposure, especially at internal field strengths too low to produce heat at biologically significant rates.

As indicated previously, RFR pulses of appropriate characteristics are known to be perceived by some humans as apparent sound (the "RFR-auditory effect"). Pulsed RFR has also been reported to produce other effects, such as alterations of the blood-brain barrier and behavioral changes. Some researchers, using RFR that was amplitude-modulated at specific frequencies, primarily below about 30 Hz but up to about 400 Hz, have reported biological effects from the amplitude modulation per se, notably the "calcium-efflux" effect. Such reports are regarded by some researchers as evidence for the existence of nonthermal RFR bioeffects. These topics are discussed more fully later.

2.5 RFR AND FIELDS AT POWERLINE FREQUENCIES

Worth mentioning under the heading "nonionizing fields" are several kinds of electric and magnetic fields. Such fields occur both naturally, among them the earth's magnetic field and the electric fields in the atmosphere (most prominent during storms), and by generation for various uses. Regarding the latter, much controversy currently exists regarding reports of deleterious effects on humans from exposure to the electric and magnetic fields present within homes from the power lines supplying electricity to the house, the fields from operating appliances within the home, and those from any nearby high-tension power lines. In considering possible bioeffects of the RFR from any specific system, it is important to recognize the distinction between such powerline fields and the RFR emitted from such systems, as discussed below.

Powerline sources in the U.S. operate at 60 Hz. The corresponding wavelength is more than 3,000 miles, meaning that people near a powerline are in its "induction zone," within which terms such as "propagation" and "radiation" do not apply. Rather, the electric and magnetic fields from such a source may induce currents in the body that alternate in direction at the 60-Hz rate, and the effects of each field should be considered separately.

At 3.0 GHz, for example, which is 50 million times higher than 60 Hz, the corresponding wavelength is only about 4 inches. Thus, sources operating at such frequencies emit and propagate electromagnetic fields as true radiation even at short distances therefrom. In such radiation, the electric and magnetic components are at right angles to one another and to the direction of propagation. Also, the ratio of the intensity of the electric component to that of the magnetic component has a constant numerical value, so the intensity of the RFR can be stated in terms of the intensity of either component alone.

Based partly on the foregoing, a major difference between powerline and microwave fields is the way in which each interacts with a biological body with regard to penetration and absorption. In any small region within the body, each field adds to, and subtracts from, at the 60-Hz rate, the internal fields existing in that region in the absence of the external fields. A 60-Hz electric field is attenuated internally by 100,000 to a million times by the dielectric properties of the body's constituents. On the other hand, a 60-Hz magnetic field pervades the body with little if any change, and it is appropriate to consider the currents induced in the body by such magnetic fields. Whether such 60-Hz electric or magnetic fields can cause biologically significant effects depends largely on how much they alter the body's intrinsic electric fields or currents.

By contrast with the thousands of studies on biological effects at RFR frequencies, those thus far at powerline frequencies are relatively few in number and many of those are epidemiologic. Especially alarming to the general public is the reported statistical association between exposure to 60-Hz or 50-Hz magnetic fields and the incidence of one form or another of cancer or of deleterious effects on the unborn child. A close examination of those studies shows the findings to be questionable at best, *because the association is not statistically significant with measured magnetic fields*, but is

significant only with respect to the current-carrying capacity of wiring configurations and powerlines in the vicinity. Like those of RFR-epidemiologic studies, there are problems regarding the unwarranted assumptions made by the epidemiologists about the levels of the powerline fields and exposure durations, and the failure to adequately consider other environmental factors that may have contributed to the findings.

In the view of several analysts, the reported findings are not strong enough to warrant a positive statement that such effects are real, but that the possible existence of such effects cannot be dismissed either. All seem to agree that additional but more definitive studies are desirable.

3. PRESENT STATE OF KNOWLEDGE ABOUT BIOLOGICAL EFFECTS OF RFR

Most evidence for biological effects of RFR is derived from results of experiments in which various mammals (including human volunteers) and nonmammals such as birds, insects, and bacteria or other microorganisms were exposed to RFR, and specific biological effects were sought. Also studied were tissues such as excised organs and neurons artificially kept alive (*in vitro*), blood, single cells, cultures of cells, and subcellular components. Evidence is also derived from epidemiologic and occupational studies, but such results are regarded as indirect or inferential because the RFR-exposure levels and their durations most often are not known with any degree of accuracy. Epidemiologic and occupational studies are considered first.

3.1 STUDIES OF HUMANS

3.1.1 EPIDEMIOLOGIC/OCCUPATIONAL STUDIES

Epidemiologic studies are those in which the investigators seek to ascertain whether one or more health-related conditions are statistically associated with purported or actual exposure of segments of the general public to an agent (such as RFR), as distinct from determinations based on extrapolation of results with animals to humans. For epidemiologic studies with RFR as the agent, the exposure characteristics (frequencies, levels, and exposure durations) are usually surmised or are coarsely estimated.

Often open to question is the extent to which the group of humans selected as unexposed controls matches the RFR-exposure group in all relevant factors except exposure, and whether unknown or uncontrolled non-RFR factors have substantially contributed to the results. Similar remarks are applicable to studies of occupational exposure, possibly except those in which the exposures could be characterized better. In some epidemiologic studies, job title is used as the basis of estimating exposure, with varying degrees of uncertainty.

Robinette and Silverman (1977) chose 19,965 men who had served in the Navy during the Korean War who were regarded, from their titles of Electronics Technician, Fire Control Technician, or Aircraft Electronics Technician, as electronic-equipment-repair technicians and thus assumed to have had occupational exposure to RFR. For the control group, the authors selected 20,726 Naval men with the titles Radioman, Radarman, or Aircraft Electrician's Mate who thus were considered electronic-equipment operators and presumably

have had little occupational exposure to RFR. The records of the men in both groups were compared for mortality, in-service morbidity, morbidity in Veterans Administration hospitals, and granted and disallowed requests for disability compensation.

The decedent data showed no significant difference between exposed and control groups in deaths from all causes; also, the numbers of deaths in both groups were significantly lower than for the corresponding groups of age-specific white males of the general population. The death rate from trauma was significantly higher in the exposed than in the control group. When deaths from trauma were subdivided into motor-vehicle and "other accidents", suicide, and homicide, the only significant difference between exposed and control groups was in the "other-accident" category. In that category, however, the death certificates and the other mortality data about the men in the exposed group showed that many had died in military-aircraft accidents after the Korean War, presumably because more of them later became flying officers. Thus, no statistical association was found between health effects and presumed RFR exposure.

The U.S. Embassy in Moscow was irradiated with low-level RFR from 1953 until February 1977. Lilienfeld et al. (1978) conducted a study on the health of U.S. personnel assigned to the Moscow embassy during that period. The authors identified 1,827 employees and 1,228 dependents as having been at that embassy during the 1953-1976 period. The controls comprised 2,561 employees and 2,072 dependents assigned to embassies and consulates in Budapest, Leningrad, Prague, Warsaw, Belgrade, Bucharest, Sofia, and Zagreb during the same period. Periodic tests for RFR at those control sites showed only background levels.

Medical records were reviewed for 1,209 of the Moscow employees and 834 of their dependents. The respective numbers for the control group were 1,882 and 1,507. Health questionnaires were returned by 969 Moscow employees and 1,129 control employees. The number of questionnaires completed by the dependents was not clearly indicated in the report.

The questionnaire data indicated higher incidences of some health problems in Moscow employee groups than in controls: more correctable refractive eye problems; more cases of psoriasis in men; more cases of anemia in women; and more frequent cases of depression, irritability, difficulty in concentrating, and memory loss. The authors noted: "In view of the possibilities which had been publicized of the increased danger to their health and that of their children, it is not at all surprising that the Moscow group might have had an increase in symptoms such as those reported. However, no relationship was found between the occurrence of these symptoms and exposure to microwaves; in fact, the four symptoms mentioned earlier, which showed the strongest differences between the Moscow and Comparison groups, were all found to have occurred most frequently in the group with the least exposure to microwaves."

No discernible differences were found between Moscow and control groups in total mortality or mortality from specific causes, nor were there mortality differences between Moscow and control groups of adults or dependent children. The mortality rates for the Moscow and control groups were lower

than for the U.S. population at large, except for cancer-related deaths, which were fractionally higher among Moscow-female (8 of 11 deaths) than control-female employees (14 of 31 deaths). The authors stated: "It is difficult to attach any significance to the relatively proportion of cancer deaths in females because of the small numbers of deaths involved."

The authors recognized and commented on limitations of this study due to their inability to acquire complete sets of medical records, death certificates, and returned health questionnaires, and to the imprecision in classifying individual employees with regard to probable extent of RFR exposure. They also noted that for many of the medical conditions studied, the sizes of the study populations were too small for detecting less than twofold excess risks. In addition, they indicated that highest RFR levels were recorded late in the period of irradiation and therefore, for the subgroup with the highest potential exposure, the period of time during which health effects might have become apparent was the shortest. However, despite these acknowledged limitations, the authors were able to draw the following conclusions.

For dependents, the authors found no differences between adults in the Moscow and control groups. The incidence of mumps in Moscow-based dependent children was twice that in control children. The incidences of congenital anomalies in children born after arrival of the parents at their duty stations were comparable for the Moscow and control groups.

The authors concluded: "With very few exceptions, an exhaustive comparison of the health status of the State and non-State Department employees who had served in Moscow with those who had served in other Eastern European posts during the same period of time revealed no differences in health status as indicated by their mortality experience and a variety of morbidity measures. No convincing evidence was discovered that would directly implicate the exposure to microwave radiation experienced by the employees at the Moscow embassy in the causation of any adverse health effects as of the time of this analysis."

In one of a pair of studies, Lester and Moore (1982a) endeavored to establish an association between mortality from cancer and proximity of the decedents to Air Force bases. Polson and Merritt (1985) found this study to be flawed by incorrect assembly of the data base. When they independently assembled the data base correctly and analyzed it, they found that the cancer incidence for either sex in counties that had Air Force bases did not differ significantly from the incidence in counties that did not have Air Force bases.

In the second study, Lester and Moore (1982b) sought to determine whether there was a geographic pattern of cancer incidence within the city of Wichita, Kansas, and whether specific sources of RFR could be identified and related to any such pattern. They reported finding a neighborhood pattern of cancer incidence, with a suggestion of a time element in its appearance, and noted that cancer tended to occur for persons located on leading terrain crests relative to radar transmissions and occurred less frequently in the valleys.

They derived a formula relating cancer incidence to the terrain and presence of RFR, leading to the overall finding that cancer incidence in Wichita appears to be related to the probability of RFR exposure from the radars at Wichita Mid-Continent Airport 9.7 km southwest and 35 ft high, and McConnell Air Force Base 7.2 km southeast and 130 ft high, both sites relative to the city center. The formula apparently bore no relation to actual exposure levels; the authors did not cite measurements to support their assumptions and gave no indication that the scan sectors of such radars were considered. A model of RFR exposure should have been used that is based on the physical laws of RFR propagation, particularly the inverse-square-law of attenuation with distance and the RFR shielding by artificial structures as well as terrain. Thus, any conclusions drawn in the paper are unwarranted.

Hamburger et al. (1983) noted that physical therapists are known to use various diathermy modalities (which they characterized as "microwave, shortwave, infrared, and ultrasound equipment") in the course of treating patients. They therefore sought to determine whether therapists might be suffering adverse health effects from exposure to the emissions from such units on a dose-related basis. They statistically analyzed the responses from male members of the American Physical Therapy Association (APTA) to a mailed questionnaire. The only consistent statistically significant finding was an apparent association between heart disease and exposure to shortwave radiation.

Although the authors considered other factors in the questionnaire, they emphasized those health experiences reported in the RFR-bioeffects literature as being associated with exposure to low levels of RFR. The responses requested from each subject included occupational history of diathermy utilization by length of employment in each position held since entering the clinical affiliation, and the number of treatments of each modality administered per typical work week. Other factors considered were the frequency of treatments, the years of work experience, and the use of infrared and ultrasound diathermy.

Three mailings of questionnaires were made, to reduce the number of nonresponses. The final population sample consisted of 3004 respondents from a total of 5187 therapists solicited. The respondents were divided into subgroups according to exposure across and within the energies of the four modalities above. The modalities were coded as U (ultrasound), I (infrared), M (microwave), and S (shortwave), and the authors initially distributed the population among the 15 exposure subgroups consisting of those exposed solely to each modality and those exposed to all possible combinations thereof, plus a group that was not exposed. However, the small sizes of several groups necessitated merging them into other groups to ensure more meaningful statistical results, yielding nine subgroups.

Selected characteristics of the respondents were tabulated for the nine subgroups (age, race, marital status, present work setting, personal therapy with any modality, X-ray exposures) and prevalence among them of the following reported conditions: blood disorder, cataracts, diabetes, endocrine disorder, hearing disorder, heart disease, high and low blood pressure, nervous breakdown, and "other".

The authors found that the reported prevalence rates for the entire cohort were below population rates in all instances, and that no single subgroup showed markedly higher rates relative to total rates. However, they noted that the all-four-modalities subgroup had significantly higher heart disease rates than those for the remaining population. They then formed new subgroups: microwave, shortwave, and joint microwave/shortwave exposure, and further divided them into high- and low-exposure groups. A respondent with any exposure to microwave was included in the microwave group. Similar definitions were used for shortwave and joint exposure so the subgroups were not mutually exclusive, resulting in double-counting of subjects, a point recognized by the authors.

Contingency tables were constructed for the three types of exposure and for the three high-exposure versus low-exposure situations (treatment frequency, length of employment, and combination thereof), comprising 3x3 or nine contingency tables for each of the 10 medical conditions, for a total of 90 contingency tables. The odds ratios for high exposure versus low exposure in the three exposure categories were also calculated for each contingency table, and the confidence intervals were determined for the odds ratios that were statistically significant after age adjustment. Heart disease was the only condition that remained significant, and only in four of the nine type-of-exposure versus high-low situations, i.e., in 4 of the 90 contingency tables, a finding that is no better than chance.

The findings above may be cited by some as "proof" that exposure to microwave/shortwave RFR causes heart disease. However, careful analysis of the paper did not yield convincing evidence that this is so. First, the paper illustrated the problems associated with attempts to uncover causal relationships between a purported health-effects agent (RFR in this case) and medical conditions in an identified population by using only the responses to a mailed, self-administered questionnaire. The response rate was 58%, so 2,183 persons did not respond. The authors did not mention any attempt to reach a sample of nonrespondents by telephone or in person, to endeavor to characterize them as a group. (There exist statistical techniques to correct for bias when the nonrespondents group is large.) The 58% that did respond were self-selected in the sense that many of them may have responded because they had medical conditions and were curious about how such conditions may have arisen.

The major finding, that there is a statistical link between heart disease and self-reported recollection of one aspect of occupational exposure (frequency or number of treatments/week, but not employment duration) to shortwave and microwave radiation (the latter downplayed), but not to joint shortwave/microwave exposure, is weak at best. If the results are taken to mean that shortwave exposure is a causal agent but joint shortwave/microwave exposure is not, it also could be inferred that microwave exposure protects against possible adverse effects of shortwave exposure with respect to heart disease, a most unlikely conclusion. In addition, duration of employment, which normally would be considered a factor in "cumulative exposure," had no statistically significant role.

On the basis of the RFR-bioeffects literature, the authors had classified heart disease into: (1) disorders of conduction/rhythm and ischemia

and (2) "other" and found statistical significance only for the first category. Heart disease, however, comprises many symptoms having various etiologies. For example, cigarette smoking is a widely known major risk factor and a strong predictor of heart disease in an aging population such as the 35+ group in the present study, for which the relationship with shortwave exposure was claimed. Inexplicably (but acknowledged by the authors), smoking history was not included in the questionnaire. Failure to consider this major biasing factor does not inspire great confidence in the sole positive finding of this study.

Milham (1983) analyzed the information on age and year of death in Washington State of 429,926 male decedents for 1950-1979 and 25,066 female decedents for 1974-1979, and presented cause-of-death analyses (160 causes) for 219 male and 51 female occupational categories. One finding was an increase in leukemia in workers exposed to electric and magnetic fields.

The statistic used by the author was the "proportionate mortality rate [or ratio]" (PMR). By definition, the PMR for each cause of death is the ratio of the number of deaths for that cause to the number of deaths from all causes, expressed as a percentage, so the sum of all PMRs must be 100. Epidemiologists Lilienfeld and Lilienfeld (1980) state (pp. 74-75):

"The proportionate mortality rate does not directly measure the risk or probability of a person in a population dying from a specific disease as does a cause-specific mortality rate."

They illustrate the point with a simple example in which the death rates from cardiovascular diseases in two counties are the same but the death rates from all causes differ considerably, thus yielding much different PMRs for cardiovascular diseases in the two counties. More commonly used is the "standardized mortality ratio" (SMR) [see Lilienfeld and Lilienfeld, 1980, pp. 78-80]. For each cause, it is the percentage of actual deaths relative to the expected number of deaths (independent of any other SMR).

The Milham report had 63 pages of one-paragraph commentaries that described the mortality pattern in each occupation as seen by the author. Some of the commentaries appeared to be highly subjective and to reflect his personal biases. Other commentaries seemed to include elevated but statistically nonsignificant PMRs in specific occupations because the author apparently believed that those PMRs contributed to the overall mortality pattern he considered appropriate for that occupation. For example, he listed 104 deaths under the "Dieticians and Nutritionists" category. Of this total, he selected 17 and presented them as though women in this category might be expected to die more often of malignant neoplasms of the digestive organs and diabetes mellitus; the other 87 deaths were ignored.

The author examined the mortality patterns in selected occupations that appeared to have similar environmental exposures. It is only here that the categories of workers presumed to be occupationally exposed to magnetic and/or electrical fields were juxtaposed, and the PMRs for two categories of leukemia (acute leukemia, all leukemia) were given. The 11 occupations were: electrical engineers, electronic technicians, radio and telegraph operators, electricians, power and telephone linesmen, TV and radio repairmen, movie

projectionists, aluminum workers, streetcar and subway motormen, power station operators, and welders and flame cutters.

Of the 22 categories (two leukemia categories in 11 occupations), 3 PMRs were high at the 1% significance level and 2 PMRs were high at the 5% significance level. Of the remaining 17 PMRs, 13 were elevated, 3 were depressed, 1 was unchanged, but none was statistically significant. As noted above, since the sum of PMRs for all occupations must be 100, the 5 significantly high PMRs might have been a consequence of abnormally low PMRs in three of the 11 occupations, a point explicitly recognized by the author. Thus, little credence can be given to the author's claim that the higher PMRs for acute leukemia and all leukemia are associated with exposure to electric and magnetic fields.

Another point to be considered is that a dose-response relationship must exist in order to conclude that cause-and-effect applies in this or any other epidemiologic/occupational study. Such a relationship was not established in this study. Without exposure data for the individuals or even for the occupations, there is no evidence that persons in these 11 occupations did receive more exposure to electrical and magnetic fields than those in other occupations. To illustrate this point, electricians, the occupation with the largest number of leukemia deaths (51), do spend a large part of their time working on circuits that are not energized.

In a subsequent study, Milham (1988) examined mortality data for amateur radio operators presumed exposed to RFR while operating their transmitters. He extracted the names of 67,829 males in Washington State and California listed as licensed in the 1984 U.S. Federal Communications Commission Amateur Radio Station and/or Operator file between 1 January 1979 and 16 June 1984. Those names were searched for deaths during the five-year period from 1 January 1979 to 31 December 1984, which yielded a total of 2,485 male decedents taken to have had 232,499 person-years at risk. Herein, the author did use the standardized mortality ratio (SMR).

The total number of expected deaths in both states from all causes was 3,479, so the 2,485 deaths of licensees yielded an SMR of 71, with a 95% confidence interval of 69-74, indicating significantly lower death rates for licensees than for the general population. The category "all circulatory diseases" yielded the largest number of deaths, 1,208, but 1,732 were expected, so the SMR was only 70 (95% confidence interval: 66-74), also indicating a significantly lower death rate than in the general population.

The category "all malignant neoplasms" had 741 deaths versus 839 expected, yielding an SMR of 89 (95% confidence interval: 82-95), again a significantly lower death rate than for the general population. The only subcategory of malignant neoplasms that yielded an SMR that significantly exceeded 100 was "other lymphatic tissue". There were 43 deaths versus 27 expected; the SMR was 162, with a 95% confidence interval of 117-218. The subcategory "leukemia" had 36 deaths versus 29 expected, for an SMR of 124, but the 95% confidence interval was 87-172, thus rendering this result nonsignificant. The author considered nine subdivisions or sub-subdivisions of "leukemia" and found that of the 36 deaths, 15 were for "acute myeloid" leukemia versus 8.5 of the 29 expected. These values yielded an SMR of 176

with a 95% confidence interval of 103-285 for an apparently statistically significant result. However, little if any credence can be given to this finding, in view of the small numbers of deaths relative to the actual and expected totals. Thus, despite any claims to the contrary by the author, the results of this study do not offer any confirmation of those in Milham (1983).

Thomas et al. (1987) performed an analysis of brain tumor mortality risk for men occupationally exposed to RFR, lead, and soldering fumes in the petrochemical industry. They obtained death certificates of men who had died at age 30 years or older from brain tumors or other tumors of central nervous the system between 1 January 1979 and 31 December 1981 in northern New Jersey and in Philadelphia and its surrounding counties. They also acquired similar data for men who had died between 1 January 1978 and 30 June 1980 in the gulf coast of Louisiana. The lifetime work histories for the case men were obtained from next-of-kin. One control for each case was selected from men matched in age and year of death and area of residence, but who had died from causes other than brain tumor.

Case men were classified regarding RFR exposure by two methods. In the first method, the men were divided into two job-related categories: those involved in the design, manufacture, installation, or maintenance of electronic or electrical equipment; and those exposed to RFR in other types of jobs (such as welding and radio broadcasting). In the second method, a certified industrial hygienist independently assigned codes to each job in the lifetime occupational histories for presumed exposure to RFR, to lead (high, moderate, low), and to soldering fumes (high, low). The authors noted that the classifications for RFR exposure in the two methods overlapped considerably, but that the second method included men in supervisory jobs not considered exposed in the first method.

Information was available on 435 cases and 386 controls. Of the 435 cases, 300 had astrocytic tumors, 90 had other recognized types of tumor cell, and 45 had unknown types of tumor cell. The authors estimated the maximum-likelihood relative risk (RR) and 95% confidence interval (CI) for each exposure and job category, and adjusted the data for potential confounding influences of educational level. They regarded any RR as statistically significant if its 95% CI did not span 1.0.

The analyses showed significantly elevated RRs for astrocytic brain tumor among men classified as exposed to RFR in jobs involving design, manufacture, installation, or maintenance of electronic or electrical equipment. RRs were not elevated for exposure to RFR in other types of jobs. The highest RR was for the combined classifications of engineers, teachers, technicians, repairers, and assemblers. RR rose with exposure duration to tenfold for those in jobs associated with the manufacture and repair of electronics for 20 or more years, but the RR for "tradesmen" (combined categories of electricians, and power and telephone linemen) showed no consistent pattern with increasing employment duration. On the other hand, the RRs were also higher for electronics workers classified as not having been exposed to RFR.

Elevated RRs were reported for those exposed to soldering fumes, but the variations with presumed exposure level were not large. However, nearly

all of the men exposed to soldering fumes had such exposure in electronics manufacture and repair jobs. RRs were not elevated for lead exposure by level (low, medium, high) or overall.

Based on the results, the authors suggested that simple exposure to MW/RF radiation is not the responsible agent for excess brain tumor risk, and noted that exposure to such radiation in electronics jobs is probably intermittent and may be accompanied by exposures to lead, solder fluxes, solvents, and other chemicals. They also stated that the results should be interpreted with some caution, because when they calculated the risks for specific occupations and for individual strata by duration employed, they obtained very small numbers in single cells.

Burr and Hoiberg (1988) compared the hospitalization rates of 1,063 Naval pilots, who primarily flew "electronically modified aircraft" (the test group), with an age-matched control group of 2,126 pilots who flew other aircraft. A major difference between the two groups was that the pilots of the test group were presumed to be subject to greater potential risks from exposure to ionizing radiation (such as at high altitudes) and nonionizing radiation (such as from the onboard antennas and electronic equipments) than the control group.

The results showed that in the age range 21-26 years, control pilots had a significantly higher mortality rate for aviation-related injuries and higher hospitalization rates for accidents, poisonings, and violence than those in the test group. Also, in the age range 27-32 years, the pilots in the control group had a significantly higher hospitalization rate for mental disorders. The authors noted, however, that neither group had any hospitalizations for conditions related to either ionizing or nonionizing radiation.

Wertheimer and Leeper (1979) sought for and found statistically significant correlations between 60-Hz wiring configurations of homes in the Denver area and previous occurrence of cancer in children dwelling therein. The study was criticized for the absence of measurements of the fields in those homes, the possible presence of other agents known to contribute to cancer incidence, and possible bias because the researchers had known which homes had the cancer victims.

Savitz et al. (1988) did a similar but blind study on a different population in Denver. Those researchers measured the magnetic field at various locations within homes and did find a statistically significant correlation between the incidence of childhood cancer and proximity of their homes to wires carrying high currents. However, the association between the incidence of cancer and the magnetic fields actually measured was weaker than reported by Wertheimer and Leeper and was within the margin for measurement error. Again it was suggested that agents other than the magnetic fields may have been responsible.

Various other epidemiologic studies have been done on a possible association of cancer and exposure to powerline fields, particularly the magnetic fields. Taken collectively, the findings of those studies are

inconclusive and there is a consensus that further research is needed to determine whether such a linkage is real.

The EPA issued a preliminary report for external review (EPA, 1990) indicating a possible link between exposure to electromagnetic fields (RFR as well as those from powerlines) and cancer. Recommended in the report was that electromagnetic fields in the extremely low frequency (ELF) range be classified as "probable human carcinogens," in a class with PCBs, DDT, and formaldehyde [see MICROWAVE NEWS, May/June 1990]. Also recommended in the report was that RFR be designated as a "possible" carcinogen, in a class with saccharin.

The director of the EPA office that prepared the report ordered the ELF recommendation deleted in the absence of a mechanism of interaction and a dose-response relationship, and also deletion of the recommendation regarding RFR. Thus, stated in the preface dated 13 December 1990 to the October 1990 draft of the report were the following:

"While there are epidemiological studies that indicate an association between EM fields or their surrogates and certain types of cancer, other epidemiological studies do not substantiate this association. There are insufficient data to determine whether or not a cause and effect relationship exists."

"Given the controversial and uncertain nature of the scientific findings of this report and other reviews of this subject, this review draft should not be construed as representing Agency policy or position."

Accounts of other activities regarding the EPA report, including comments by various individuals on both sides of the controversy, are contained in subsequent issues of MICROWAVE NEWS. Among the latest actions to date [MICROWAVE NEWS, September/October 1991] was that the Committee on Interagency Radiation Research and Policy Coordination (CIRRPC) of the White House Office of Science and Technology Policy (OSTP) has urged the EPA to overhaul the report, a recommendation similar an earlier one by EPA's Scientific Advisory Board (SAB).

3.1.2 CONGENITAL ANOMALIES

Two studies were done that sought a possible relationship between the occurrence of Down's syndrome and presumed exposure of the fathers to RFR from radars during military service. In the first study, Sigler et al. (1965) examined the data, derived from Baltimore hospital records and interviews with parents, on 216 Caucasian children with Down's syndrome. The case children were matched with 216 control children for hospital of birth (or birth at home), sex, and birthdate (within 6 months), and nearly all were matched for maternal age (within 1 year) at time of birth. The parents were also matched for birthplace, residence, and hospital treatment.

Irradiation histories of the mothers were categorized as: diagnostic radiation excluding fluoroscopy, fluoroscopic exposure, radiation for therapy, and occupational contact. One statistically significant finding was that the percentage of case mothers that had received fluoroscopic examinations before

the birth of the case child was significantly higher than for the control mothers. The percentage of case mothers who had at least one therapeutic radiation exposure (mostly for skin ailments) and the percentage of case mothers who worked in a professional or technical capacity in medical fields were also significantly higher than for the control mothers.

The difference in the percentages of case and control fathers that had served in the military was nonsignificant, but a higher percentage of case fathers reported close association with radars as technicians or operators than the control fathers. The authors thus ascribed the higher incidence of Down's syndrome primarily to greater exposure of the case mothers to ionizing radiation, but concluded: "The only truly puzzling association is the suggested relationship between Mongolism [Down's syndrome] and paternal radar exposure."

In the second study, Cohen et al. (1977) reexamined the data in the first study, denoted as the "Original Series," along with the data on 128 additional matched pairs denoted as the "Current Series". They concluded that the findings for the Current Series did not confirm the suggestions that the fathers of the children with Down's syndrome previously did have excess radar exposure or a larger proportion of military experience.

Peacock et al. (1971) endeavored to assess whether the incidence of birth defects in Alabama could be associated with proximity of military bases. They examined a state-wide file of birth certificates by counties and found an overall rate of 10.3 newborns with anomalies per thousand births, comparable to rates in other registries. A more detailed study of the data showed that there were 17 anomalies per thousand births for the military personnel in the six-county area surrounding Fort Rucker. By contrast, the anomaly rate for civilian births was 6.8 per thousand.

Peacock et al. (1973) reassessed the premise, but with data spanning four years rather than the 17 months examined previously. Also, the data were corrected and rendered more accurate than previously, and a more precise test of the reliability of inferences was performed that did not rely on the questionable use of a normal approximation. After accounting for "non-radar" factors, the authors repeated the analyses for the Fort Rucker area and specifically for Lyster Hospital (within Fort Rucker). In addition, as a "control" test, they compared the fetal death anomaly rates in the military hospitals at Fort Rucker and Eglin Air Force Base (which they designated as "radar bases") with those of three military hospitals in bases with minimal radar networks.

The results of the retests confirmed that the total anomaly rate and the rates for several specific anomalies were abnormally high at Lyster Hospital. Also, the numbers of fetal deaths for Lyster hospital and the hospital at Eglin Air Force Base were comparable and "constitute evidence that the problem may be associated with radar".

Burdeshaw and Schaffer (1977) reexamined the original Alabama birth records, but compared the data for Coffee and Dale Counties (within which Fort Rucker is located) with the data from each of the other 65 counties in Alabama on a score and rank basis instead of the statewide averages. They found

little evidence that the incidence of congenital anomalies in the Fort Rucker area was unusually high. The overall rate at Lyster was well within the expectations for hospitals with characteristics similar to those of Lyster. When the addresses of mothers of anomalous infants were plotted on county road maps, no significant clustering was found, particularly in the vicinity of presumed radar sites.

Källén et al. (1982) hypothesized that physiotherapists (in Sweden) were likely to have been occupationally exposed more to various agents (chemicals, drugs, X-rays, RFR) than the general population. Therefore, they did a cohort study on 2,043 infants born during years 1973 to 1978 to 2,018 women registered as physiotherapists during their pregnancies. By crosslinking files in two major computer-based registers, the authors were able to identify infants of mothers registered as physiotherapists at delivery time. They then analyzed this cohort for perinatal mortality and the presence of malformations by comparing the data with information on all deliveries in the Swedish Medical Birth Register.

The results showed that for all endpoints, the expectation values for the total cohort were statistically better than, or comparable to, those for the general population. The authors noted that this excellent outcome could have been the result of a "healthy worker" effect, so they hypothesized that if hazardous exposure exists, it should be more common among the few females who had dead or malformed infants than among those who had normal babies. Accordingly, they did a case-control study within the cohort, in which they selected 37 infants who had major malformations or those that did not but had died perinatally. Each infant was compared with two normal infants matched for maternal age, parity, and season of delivery (to compensate for work seasonality). Exposures for the case and control mothers were estimated from the answers to a questionnaire that asked (in part):

"Did you, during the pregnancy, work with or in close proximity to the following:

Shortwave equipment: daily/often/seldom/never
Microwave equipment: daily/often/seldom/never
Ultrasonic equipment: daily/often/seldom/never
X-Ray equipment: daily/often/seldom/never
Electrostimulator: daily/often/seldom/never

"Did you use hexachlorophene-containing soap (e.g., Phisohex): daily/often/seldom/never"

On careful review and interpretation of the results, they concluded that the physiotherapists as a group had a slightly better-than-expected outcome for perinatal deaths and major malformations than did the general Swedish population for the same period. They did report that the use of shortwave equipment was higher among those who gave birth to a malformed or perinatally dead infant. In a critique of the paper, however, it was pointed out that those results would change from borderline significance to nonsignificance if one or two answers to the questionnaire were based on faulty recall.

In summary, Sigler et al. (1965) had obtained results suggestive of an association between the occurrence of Down's syndrome in children with radar exposure of the fathers during military service. However, the study by Cohen et al. (1977) with a larger data base yielded negative findings, thereby superseding those of the earlier study. Similarly, the negative findings of the study by Burdeshaw and Schaffer (1977) on the incidence of birth defects from proximity to military bases superseded those of the two studies by Peacock et al. (1971,1973).

The Källén et al. (1982) study on infants born to physiotherapists presumed to have been occupationally exposed to various agents such as chemicals, drugs, X-rays, RFR actually yielded fewer dead or malformed infants than in the general population. The data base for the cohort part of the study was large, thereby yielding statistically credible negative findings. However, the use of a questionnaire in the case-control part of the study renders questionable the finding of a weak association of malformed or perinatally dead infants with the use of shortwave equipment.

3.1.2.2 CONCLUSION

Thus, the studies on congenital anomalies or perinatal infant deaths have not yielded any scientifically valid evidence that such effects are caused by chronic exposure to RFR at levels below the U.S. exposure guidelines.

3.1.3 OCULAR EFFECTS

The cornea and lens are the regions of the eye most vulnerable to RFR at high levels by their surface location and because any heat produced by the RFR is more effectively removed from other regions, particularly by blood circulation. Indeed, there have been several documented early cases of inadvertent exposure to RFR at levels high enough to cause cataracts, and appropriate safety measures have been taken to avoid such exposure.

3.1.3.1 EYE DAMAGE BY RFR IN ANIMALS

It is more convenient to discuss relevant studies on the effects of RFR on the eyes of animals here (under "Studies of Humans") than in the sections of this document on animal studies. Many such investigations with animals have been performed during the past several decades, most of them with rabbits, but several with primates.

Carpenter et al. (1960) exposed predominantly the right eyes of 136 rabbits to 2.45-GHz CW RFR, one each at a level in the range 120 to 400 mW/cm^2 for respective durations of 60 to 10 minutes. After exposure, both eyes of each rabbit were examined at regular intervals with an ophthalmoscope and slit-lamp microscope.

The unexposed left eye of each rabbit was found to be clear in post-exposure followup examinations. Level- and duration-dependent degrees of opacity were observed in the exposed right eyes for some exposure conditions. Those opacities were uniformly located in the posterior subcapsular cortex

(PSC) and first appeared within 1 to 6 days after exposure, with a mean latency of 3.5 days.

The outcome of each exposure condition was shown as a circle on a graph of power density versus exposure duration, with solid circles for those that yielded lens opacities and open circles for those that yielded no effect. A curve that connected the circles representing the shortest duration at each power density that caused the development of an opacity was taken as the relation between the threshold power density for opacity induction by a single exposure versus exposure duration. Ths curve was a rectangular hyperbola, indicative of reciprocity (inverse relationship), with a non-zero power-density offset (asymptote) for exposures of long durations. The threshold exposure durations at 400 and 120 mW/cm^2 were about 3 and 35 minutes, respectively, with intermediate durations for power densities between those two values. By extrapolation beyond 60 minutes, the asymptotic threshold power density was roughly 80 mW/cm^2.

In a later study, Carpenter and Van Ummersen (1968) exposed one eye each of anesthetized rabbits to 8.2-GHz or 10-GHz RFR, also for a range of durations and input powers (power densities not indicated), and used the results to derive threshold-power versus exposure-duration curves for those frequencies. The curves at 8.2 and 10 GHz were similar to each other and to the curve for 2.45 GHz, but with an asymptote of 650 mW. For exposures to 8.2 and 10 GHz above threshold levels, however, the cataracts always developed in the anterior cortex of the lens, whereas those for 2.45 GHz were typically located in the posterior cortex.

Guy and coworkers did similar experiments at 2.45 GHz and obtained similar results, including threshold curves of incident power density versus exposure duration. As reported in Guy et al. (1975a), their threshold for exposure durations of 100 minutes (or longer) was roughly 150 mW/cm^2. In addition, they obtained the following results:

(1) Increases in intraocular temperature of about 5 ^{o}C or more are necessary for thermal eye damage.

(2) Eye opacifications solely from exposure to RFR levels above the threshold are not produced at the same levels when the eye is cooled during exposure, showing that cataract causation by RFR is basically a gross thermal effect.

By contrast, Kues et al. (1985) reported that exposure of the eyes of anesthetized monkeys to 2.45-GHz CW RFR in weekly 4-hour sessions at 30 mW/cm^2 yielded moderate-to-major changes in the numbers of corneal lesions seen with a specular microscope. Such lesions within fields of 1 mm^2 were counted in photographs of the central 6 mm of cornea. The local SAR was 7.8 W/kg, determined from temperature measurements in the eyes of live monkeys. Exposures at 5, 10, or 20 mW/cm^2 (1.3, 2.6, or 5.2 W/kg) caused no damage to the corneal endothelium. Representative results were presented for one monkey given 22 weekly sessions at 20 mW/cm^2, then eight sessions at 30 mW/cm^2, and last, two series of four consecutive daily sessions at 20 mW/cm^2.

This study also appeared to indicate that 2.45-GHz pulsed RFR is more effective than 2.45-GHz CW RFR. Weekly 4-hour sessions of pulsed RFR at 10 mW/cm^2 average power density (2.6 W/kg) yielded minor or no corneal damage, but consecutive daily sessions at this level caused major damage, apparent evidence for effects of cumulative exposure. Moreover, one monkey showed major damage after only one session of pulsed RFR at 15 mW/cm^2 (3.9 W/kg).

Several representative specular micrographs were presented. Among those was one from a monkey before exposure, which clearly delineated the hexagonal cell boundaries and the nuclei of most cells, and exhibited no lesions. However, a photomicrograph, taken 48 hours after another monkey was given a single 4-hour exposure of pulsed RFR at 15 mW/cm^2, exhibited numerous lesions over areas of normal mosaic, each involving one cell or several contiguous cells. Also, a specular photomicrograph for a monkey 48 hours after a session at 10 mW/cm^2 showed a similar distribution.

The findings of this study have been questioned with regard to the adequacy of the exposure technique used and exposure of the same monkeys in more than one aspect of the study. Moreover, the results appeared to indicate that the corneal effect is reversible, even though the authors noted that the primate corneal endothelium is not known to repair itself through cell division. Resolution of such points await further studies or replication in other laboratories.

Stewart-DeHaan et al. (1985) excised the eye lenses from rats and exposed the lenses to 10-μs pulses of 918-MHz RFR at several SARs, repetition rates, and durations in a waveguide system while keeping the lenses at constant temperature. The lenses were fixed immediately after exposure, and depth of granular degeneration in the equatorial region, determined by scanning-electron or light microscopy, was taken as the extent of lens damage. The pulses had a forward peak power of 24 kW and repetition rates that yielded mean forward powers in the range 65 to 0.5 W, with corresponding SARs in the range 1,300 to 10 W/kg.

Statistical analyses indicated that lens damage increased with both exposure duration and SAR, with evidence for reciprocity. The authors stated that lens damage could be detected by scanning electron microscopy after 6 minutes of exposure at 40 and 20 W/kg, and by light microscopy after 1 hour of exposure at 10 W/kg.

Creighton et al. (1987) reported on similar experiments, but with CW as well as pulsed RFR. Again, 10-μs pulses of 918-MHz RFR at 24 kW peak power were used; these were delivered at repetition rates that yielded SARs in the range 5.75-750 W/kg and durations of 6, 20, or 60 minutes. The range of total energy deposited in the lens was 0.23-15 watt-minutes per gram (0.0138-0.90 J/kg). The results indicated that the pulsed RFR caused about 4.7 times greater depth of lens damage than the CW RFR at the same SAR for every combination of SAR and exposure duration except at 23 W/kg for 6 minutes. The authors suggested that the added damage could be ascribed to the thermoelastic effect of the pulses (Section 3.1.4).

Foster et al. (1986) exposed the heads of anesthetized rabbits for 30 minutes each to 2.45-GHz RFR at various input powers in a waveguide system.

The head of each rabbit was inserted in the waveguide with the left eye toward the RFR source. Measurements of input, reflected, and transmitted powers permitted determination of rates of energy absorption within the head. In each case, the transmitted power was negligible, so the difference between the incident and reflected powers represented the power absorbed in the head. For the same reason, the right eye received virtually no power, thereby serving as the control for the left eye.

Immediate post-exposure eye changes were noted, and each rabbit was given slit-lamp examinations for about 2 months. No changes were seen in the control eyes. The incidence of lens changes (in the left eyes) was plotted against both incident power and absorbed power (rate of energy absorption). A graphical solution for 50% incidence of opacities yielded a forward power and an absorbed power of 8.7 W and 5.75 W, respectively. For a 375-gram head, 5.75 W corresponds to a whole-head SAR of 15.3 W/kg. From measurements of rectal temperature, the authors found that 80% of the energy absorbed in the head was redistributed systemically, a finding that substantiates the concept that the thermoregulatory capabilities of an animal influence thresholds.

Since the exposures in the waveguide were to the dominant electric field (TE_{10} mode), the authors calculated the power density corresponding to the 8.7-W threshold and obtained 285 mW/cm^2. They also calculated the equivalent free-space electric-field intensity to be 704 mV/cm. Based on these values, they noted that their waveguide power-density threshold compared well with those found with other kinds of exposure systems that provided very different electric field intensities, and they concluded that the rate of energy absorption rather than the peak electric field is the significant parameter in RFR cataractogenesis.

In summary, with the possible exception of the Kues et al. (1985) study, all of the experiments with animals indicate that ocular damage by exposure to RFR is a gross thermal effect. Especially noteworthy are the findings of Guy and coworkers that exposure to RFR at levels that yield a temperature rise within the eye of about 5 ^{o}C or more are necessary for thermal eye damage and that no damage occurs from such RFR levels if the eye is cooled during exposure. Guy et al. (1975a) reported an average-power-density threshold for eye damage of roughly 150 mW/cm^2 for exposure durations of 100 minutes (or longer). A lower threshold (80 mW/cm^2) was found earlier by Carpenter et al. (1960), but errors in the power density measurements were discovered subsequently.

The results of Stewart-DeHaan et al. (1985) on exposure of excised lenses to pulsed 918-MHz RFR at SARs in the range 1,300 to 10 W/kg also comprise evidence for the thermal basis of RFR eye damage. Noteworthy is a similar study by Creighton et al. (1987) with CW as well as pulsed 918-MHz RFR, because the pulsed RFR yielded almost five times greater depth of lens damage than the CW RFR under corresponding exposure conditions.

Foster et al. (1986) used 50% incidence of opacities as a threshold criterion in rabbits whose heads were exposed for 30 minutes to 2.45-GHz RFR at various input powers in a waveguide. The result was a whole-head SAR of 15.3 W/kg (for a 375-gram head).

Kues et al. (1985) reported increases in numbers of corneal lesions observed by specular microscopy in the eyes of monkeys exposed to 2.45-GHz CW RFR at an SAR within the eye of 7.8 W/kg and not at lower SARs. The adequacy of the exposure technique used and use of the same monkeys in more than one aspect of the study have been questioned, as has the apparent reversibility of the corneal effect even though the primate corneal endothelium is not known to repair itself through cell division. Resolution of such points await further studies or replication in other laboratories.

3.1.3.2 OCULAR EFFECTS OF RFR IN HUMANS

Various epidemiologic studies expressly on possible ocular effects of RFR have been done. As with epidemiologic studies on other biological endpoints, the results were mixed. The following are representative.

Cleary et al. (1965) analyzed the incidences of cataracts in Army and Air Force veterans of World War II and the Korean War for possible association with occupational exposure to RFR. Examination of Veterans Administration hospital records produced 2,946 veterans born after 1910 who had been treated for cataracts during the period 1950-1962. A random sample of 2,164 veterans hospitalized during the same period for other ailments was selected for control. By use of the military occupational specialties (MOSs), the authors classified each person as a radar worker, a nonradar worker, or one whose specialty could not be discerned.

In the radar group, the authors found only 19 persons with cataracts and 2,625 persons without cataracts; in the nonradar group, only 21 had cataracts and 1,935 did not. (Of the other 510 veterans, 202 of those with cataracts and 125 of those without cataracts had no indicated MOSs and the remaining 100 of those with cataracts and 125 of those without cataracts had MOSs that did not permit the determination of occupational category.) Evidently, at the outset, the small numbers of persons with cataracts in both groups yielded no basis for an association between RFR exposure and cataract causation. The authors indicated that the overall relative risk factor was 0.67, as compared with 1.0 for no increase in relative risk and values larger than 1.0 representing the degree of severity of the effect.

Cleary and Pasternack (1966) analyzed responses to a questionnaire on the occupational histories of personnel then currently employed at 16 microwave installations, and used the histories to differentiate controls from exposure cases. They thereby selected 736 workers as occupationally exposed to RFR and 559 workers from the same locations and occupational environments (other than RFR) as controls. Exposure cases were grouped into occupational specialties by considering the types and functions of equipments used and the average generated powers, RFR frequencies, and modes of power termination. Exposure severity was classed by considering duration of work with each type of equipment, working distance from the equipment during normal operation, and specific type of work performed. Exposure scores were then determined by assigning appropriate weights to those factors (for example, proportionality to average power and inverse proportionality to equipment distance).

The persons in both groups were examined with a slit lamp, and each was graded for subcataractous lens changes, classified as minute defects,

opacification, reluctency, sutural defects, and posterior polar defects. A grade of 0 for "insignificant" to 3 for "large numbers or major degree of change (short of clinically recognized cataract)" was assigned in each category for each lens. An "eye score" consisting of the unweighted sum of scores for each type of defect was calculated.

A linear regression model was used for each group to relate mean eye score to age on the basis that the major increase in eye score with time was due to physiological aging of the lens. The slope of the regression line for the exposed group was significantly higher than for the control group; the lines crossed at 20 years of age with a mean score sum of 4.2. However, the authors remarked that no detrimental effects such as loss of visual acuity or higher propensity for cataract formation were associated with those subclinical eye changes, and that the results may indicate an acceleration of aging of lens tissue.

Open to question, in addition to the usual uncertainties regarding actual exposure frequencies, levels, and durations, were the grading of each worker for lens changes on an arbitrary 0-3 scale and the use of composite eye scores, measures that were subjective and not associated with actual reduction in visual acuity in the individuals examined; statistical analyses based on such measures can be misleading. Other problems were a significant difference in age distribution between the exposed and control groups and the age-related lens changes in both.

In three studies (Appleton and McCrossan, 1972; Appleton, 1973; Appleton et al., 1975), surveys were conducted of the eyes of personnel at Army posts where various types of electronic communication, detection, guidance, and weather equipment were under development, test, and use. Examinations were conducted by ophthalmologists without prior knowledge of the histories of the individuals. The visual acuity of each person was determined. Then the pupil of each eye was dilated and the fundus was examined by direct ophthalmoscopy, with particular attention on the details of the posterior pole. Recorded were the presence or absence of opacities or vacuoles and their location and number, and the presence or absence of posterior subcapsular iridescence (PSCI), a manifestation claimed by others to be associated with RFR exposure.

The authors concluded that the available clinical evidence did not support the assumption that cataracts in personnel performing duties in the vicinity of microwave generating equipment are a result of microwave exposure, unless a specific instance of severe exposure can be documented and correlated with subsequent cataract development. However, they did not present any statistical treatment of the data.

Hollows and Douglas (1984) examined the lenses of 53 radiolinemen who were occupationally exposed to RFR by erecting and/or maintaining radio, television, and repeater towers throughout Australia. The group included workers who had maximal cumulative RFR exposure but excluded those known to have cataracts or who had cataracts removed. The RFR frequencies ranged from 558 kHz to 527 MHz. Power density measurements in and around work areas yielded values in the range 0.08-4,000 mW/cm^2. The results of these

examinations were statistically compared with those for 39 age-matched controls from the same Australian states who had never been radiolinemen.

The primary ocular finding was of "posterior subcapsular cataract (PSC)" in one or both eyes of 11 of the 53 radiolinemen (21%) compared with 3 of 39 controls (8%), or alternatively in 19 of the 106 eyes (18%) of the radiolinemen compared with 6 of the 78 control eyes (8%). The first result was not statistically significant and the second was barely significant at the 5% level. The authors concluded that the excess of PSC radiolinemen may be work-related. However, the contribution of RFR exposure to those results is unclear, because nuclear sclerosis, a type of lens opacity frequently attributed to exposure to solar irradiation, was reported in 50 (47%) of the eyes of the radiolinemen and 34 (44%) of the eyes of the controls. Also, the authors did not indicate the degree of vision degradation due to PSC and/or nuclear sclerosis.

Hocking et al. (1988) sought possible effects on the health of nine radio linemen due to exposure to 4.1-GHz RFR from an open waveguide that was inadvertently activated. The men were divided into a "high-exposure" group comprising two individuals who had been exposed to 4.6 mW/cm^2 for up to 90 minutes, and a "low-exposure" group comprising the other seven men who had been exposed to less than 0.15 mW/cm^2. By calculation, upper SAR limits for the skin, pituitary gland, and whole body for the high-exposure group were respectively 3.8, 0.06, and 0.13 W/kg. The range of SAR in their eye lenses was calculated to be 1.2-1.5 W/kg.

Both men in the high-exposure group reported loosening of their scalp hair, beginning about two weeks after exposure and lasting about a month. One of these individuals claimed temporary sexual impairment and persistent symptoms of insomnia and irritability. The other individual had a moustache that was not affected.

The men in both groups were given medical examinations, their eyes were examined by ophthalmologists periodically for nine months, and blood and semen samples were evaluated. One individual in each group exhibited significant elevation of creatine phosphokinase. No other significant biochemical or hematologic abnormalities were found in the high-exposure group. Three men in the low-exposure group exhibited mild abnormalities in liver function (ascribed to alcohol).

The authors tabulated the results of the ophthalmic examinations of each subject. In the first post-exposure examination, the individuals in both groups had various eye abnormalities, but vision was normal in all. In the second post-exposure examination, eye changes were seen in both groups, but the third examination showed no further changes. The authors suggested that the changes could be ascribed to observational differences among the ophthalmologists. Their general conclusion was that the slight abnormalities seen in both groups were inconsistent and were unlikely to have been due to the RFR exposure.

In summary, the findings of Cleary et al. (1965) were negative: Of 2,644 veterans classified by military occupation specialties (MOSs) as radar workers only 19 had cataracts and 21 of the 1,956 nonradar veterans had

cataracts. The populations of the two groups were adequate in size, so the findings were negative, independent of how accurately the veterans were classified. By contrast, the findings of Cleary and Pasternack (1966) were unclear, in part because physiological aging of the lenses had occurred in both the exposed and the control groups and the two groups were not well matched in age distribution. In addition, the use of an arbitrary, subjective scale for grading lens changes and that the scale did not represent reductions in visual acuity are questionable.

The three ophthalmologic studies of Army personnel by Appleton and coworkers on possible ocular damage from exposure to RFR yielded negative findings. However, the authors used a binary (yes or no) scale to score lens damage and they gave no statistical treatment of their data. The examination by Hollows and Douglas (1984) of the lenses of radiolinemen showed some statistically significant differences in eye changes between their exposed and control groups, but the presence of non-RFR factors could not be ruled out. Also, no evidence was given that such changes affected visual acuity.

On rare occasions, cases of accidental exposure to relatively high RFR levels do occur. Hocking et al. (1988) reported on exposure of nine radio linemen to the RFR from an inadvertently activated open waveguide. In subsequent ophthalmic examinations, various eye abnormalities were seen in the "low-exposure" as well as the "high-exposure" groups, but vision was not affected in any of the subjects.

3.1.4 AUDITORY EFFECTS

Humans near some types of pulsed radar transmitters have perceived single pulses or pulse trains of RFR as audible clicks (without the use of electronic receptors). There is much experimental evidence supporting the hypothesis that an RFR pulse having a peak power density and duration within specific limits can produce a transient thermal gradient in the head large enough to generate a transient elastic wave at a boundary between regions of dissimilar dielectric properties and that this wave is transmitted by bone conduction to the middle ear, where it is perceived as a click. Persons with impaired hearing are not able to hear such clicks, and animals with destroyed cochleas (inner ears) do not exhibit RFR-pulse-induced evoked responses in the brainstem.

Frey (1961) exposed human volunteers to either 6-μs pulses of 1.3-GHz RFR at 244 pulses per second (pps) or to 1-μs pulses of 3.0-GHz RFR at 400 pps. The mean average-power-density thresholds for perception were found to be 0.4 mW/cm^2 at 1.3 GHz, and 2 mW/cm^2 at 3.0 GHz. The corresponding peak power densities were 270 and 5,000 mW/cm^2.

The author also tested four subjects having hearing loss (for air-conducted and/or bone-conducted sound) for perception of 1.3-GHz RFR. Subject 1, with both kinds of hearing loss above about 2 kHz, was unable to perceive the RFR pulses at intensities 30 times above the threshold. Subject 2, with bilateral severe air-conduction loss (about 50 dB) but moderate bone-conduction loss (about 20 dB), did perceive RFR pulses at about the threshold level. Subject 3, who suffered from tinnitus and bilateral hearing loss ranging from about 10 dB at 250 Hz to about 70 dB at 8 kHz for air conduction,

more severe loss for bone conduction, and who had been diagnosed as having neomycin-induced nerve deafness, was not able to perceive the RFR pulses. Subject 4, with normal bilateral air-conduction hearing to about 4 kHz but severe bilateral bone-conduction loss, also could not perceive the pulses.

Frey (1962) found that some subjects with an audiogram notch around 5 kHz (and adequate hearing above and below 5 kHz) did not perceive RFR pulses as sound. The author also speculated about the possible sites and mechanisms of detection, including RFR-induced changes of electrical capacitance between the tympanic membrane and the oval window, detection in the cochlea, and interaction of RFR with neuron fields in the brain. He discounted the first possibility because of insensitivity of the RFR-hearing effect to head orientation relative to the RFR source, and noted that the then-current experimental results were inconclusive with regard to the other two possibilities.

Frey (1967) subsequently tried to resolve this point by implanting an electrode in the cat brain stem and studying the potentials evoked by 10-μs pulses within the range 1.2-1.5 GHz. The results were not conclusive and may have contained artifact.

Frey and Messenger (1973) exposed humans to pulsed 1.245-GHz RFR at 50 pps in an RFR anechoic chamber. In one set, the average power density was held at 0.32 mW/cm^2 and the pulse width was varied from 10 to 70 μs in 10-μs increments, for peak power densities from 640 to 91 mW/cm^2. In another set, the peak power density was held at 370 mW/cm^2 and the pulse width was varied over the same range, for average power densities from 0.19 to 1.3 mW/cm^2. Four subjects with clinically normal hearing were each given three trials.

The results were shown as logarithmic plots of median values of perceived loudness versus peak power density and versus average power density. From their data, the authors calculated that the peak-power-density threshold for perception of RFR pulses is about 80 mW/cm^2, a value lower than those reported subsequently by Cain and Rissman (1978), discussed below.

White (1963) noted that when the surface of a body is transiently heated by RFR absorption (or electron bombardment), elastic waves are produced by surface motion due to thermal expansion. This process was analyzed theoretically, with emphasis on the case of an input heat flux varying harmonically with time, to relate the amplitude of the elastic waves to the characteristics of the input flux and thermal and elastic properties of the body. The results of experiments with both electron impact and RFR absorption verified the proportionality of the stress wave amplitude and the absorbed power density, and correlated well with the thermal and elastic properties of the heated medium.

Foster and Finch (1974) confirmed White's findings that RFR pulses can produce acoustic transients in water, and showed by calculation that for short pulses, the peak sound pressure is proportional to the energy per pulse, whereas for long pulses, it is proportional to the incident power density. Using 2.45-GHz RFR in several pulse-power-density and pulse-duration combinations and a hydrophone in saline, they found that the transition between the two regimes is for pulse durations between 20 and 25 μs. They

also found that acoustic signals were not obtained in water at 4 ^{o}C (where its thermal expansion coefficient is essentially zero) and that the polarity of the transient acoustic signal between 0 and 4 ^{o}C was reversed from that for temperatures above 4 ^{o}C. Those results support the thermoelastic expansion hypothesis.

Taylor and Ashleman (1974) surgically prepared three groups of cats for recording the potentials evoked by acoustic and RFR stimuli in three brain regions and for observing the effect of cochlear disablement. For presenting acoustic stimuli, a piezoelectric transducer was mounted on the dorsal surface of the frontal bone of each cat. In the first group, a glass microelectrode filled with physiological solution was inserted into the vestibulocochlear nerve and the round window on that side of the head was surgically exposed. In the second group, a microelectrode was inserted at a site that yielded acoustically evoked potentials, and both round windows were surgically exposed. In the third group, a Teflon-covered carbon electrode was placed on the primary auditory cortex, and both round windows were surgically exposed.

The connections to the electrodes were made with carbon leads of high resistance. The acoustic stimuli were produced by feeding 10-μs electric pulses to the transducer at 1 pps. The RFR stimuli were 32-μs, 2.45-GHz pulses at 1 pps from a horn placed 10 cm from the cat's head.

The results indicated that cochlea destruction yielded a total loss of the evoked potentials to both acoustic and RFR stimuli. The authors concluded that in animals, the transduction of RFR pulses into acoustic stimuli occurs in the cochlea in a manner similar to that of conventional acoustic stimuli.

In experiments similar to those of Taylor and Ashleman (1974), Guy et al. (1975b) studied the effect of cochlea disablement. Cats were prepared surgically for recording evoked potentials in the eighth cranial nerve, medial geniculate nucleus, and primary auditory cortex. After establishing that appropriate responses were obtained with RFR and acoustic pulses, the cochlea was disabled. This resulted in total loss of all evoked potentials, even with the highest available peak acoustic and RFR powers and with computer averaging of large numbers of signals.

Guy et al. (1975b) also determined the power-density threshold and modulation characteristics for the RFR-hearing effect in two volunteers. The authors exposed the back of the head of the two humans to RFR at 15-30 cm from the aperture of a horn in an anechoic chamber at an ambient noise level of 45 dB, with RFR-absorbent material around the vicinity of the subject to eliminate reflections. The RFR consisted of 2.45-GHz pulses of duration that was varied from 1 to 32 μs. For each duration, the RFR was presented in trains of 3 pps, with 100 milliseconds (ms) between pulses. In each case, the subject signaled when perceiving an auditory sensation. From standard audiograms taken before exposure, the hearing threshold of subject 1 was normal and subject 2 had a deep notch at 3.5 kHz in both ears for both air and bone conduction.

For subject 1, the threshold for RFR perception was found to be a constant peak energy density (product of peak power density and pulse duration) of 40 $\mu J/cm^2$ per pulse irrespective of pulse duration. At 3 pps,

the corresponding average power density was 0.12 mW/cm^2. When subject 1 wore ear plugs, the threshold peak was only 28 $\mu J/cm^2$ per pulse. The threshold for a pair of pulses spaced within several hundred μs was the same as for one pulse with the same total energy as the pair. Similar results were obtained for subject 2, but the threshold peak energy density was 135 $\mu J/cm^2$ per pulse, about threefold higher than for subject 1.

The authors noted that each pulse was perceived individually as a click and that trains of short pulses were heard as chirps of tones that corresponded to the pulse repetition rate. In addition, when the pulse generator was keyed manually, digital (Morse) code transmitted thereby could be interpreted accurately by the subject.

Cain and Rissman (1978) used 3.0-GHz RFR pulses to study the RFR-auditory effect in two cats, two chinchillas, one beagle, and eight human volunteers. For the animals, surface or brainstem-implanted electrodes were used to measure the responses evoked by audio clicks from a speaker and the responses to 5-, 10-, and 15-μs pulses.

For one cat, the threshold peak power densities were 2.2 W/cm^2 for 5-μs pulses, 1.3 W/cm^2 for 10-μs pulses, and 0.58 W/cm^2 for 15-μs pulses, and were respectively 2.8, 1.3, and 0.58 W/cm^2 for the other cat. For the beagle, the threshold values for the three pulse durations were 1.8, 0.30, and 0.20 W/cm^2. For the chinchillas, the values were 2.8, 2.0, and 0.58 W/cm^2 for one, and 2.2, 1.0, and 0.50 W/cm^2 for the other. Thus, the beagle had the lowest absolute threshold, and compared to the other animals, the lowest thresholds at corresponding pulse durations.

The eight volunteers were given standard audiograms for both air-conducted and bone-conducted sound. Also, because audiograms do not test hearing above 8 kHz, binaural hearing thresholds were determined for seven of the subjects for tone frequencies in the range 1-20 kHz. RFR pulses were presented at 0.5 pps. Each subject wore foam ear muffs during exposure, to reduce the ambient noise level, which was 45 dB.

Subjects 1-5 could hear 15-μs pulses as clicks; their peak power density thresholds were respectively 300, 300, 300, 600, and 1000 mW/cm^2. Subjects 1-5 could also hear 10-μs pulses, with peak power density thresholds of 1800, 225, 600, 2000, and 2000 mW/cm^2. The only one able to perceive 5-μs pulses was subject 1, with a threshold peak power density of 2500 mW/cm^2. By contrast, subjects 6-8 could not hear the 5-, 10-, or 15-μs pulses at the highest available peak power density but could perceive 20-μs pulses.

The authors found no correlation between the RFR results and the standard audiograms. However, they did note that a strong correlation existed between perception of RFR and hearing ability above 8 kHz as determined from the binaural thresholds. They also stated that their results are consistent with the hypothesis that an induced pressure wave in the human head in response to short RFR pulses contains a significant portion of its energy at frequencies above 8 kHz.

Thus, in the study with human volunteers by Cain and Rissman (1978), only subjects 1-3 could perceive 15-μs pulses, with a pulse-power-density

threshold as low as 300 mW/cm^2 (energy-density threshold 4.5 $\mu J/cm^2$). Only subject 2 could hear 10-μs pulses, with 225 mW/cm^2 (2.3 $\mu J/cm^2$) as the threshold; the thresholds for the other subjects were much higher than 300 mW/cm^2. Only subject 1 could hear 5-μs pulses, but with a threshold of 2,500 mW/cm^2. Those thresholds were for 45 dB of ambient noise and could be higher in noisier environments. Thus, the value 300 mW/cm^2 can be taken as the nominal human RFR-hearing pulse-power-density threshold for pulse durations of about 10 μs or longer.

It is noteworthy that Cain and Rissman (1978) had exposed the human volunteers to pulses of 3.0-GHz RFR at peak power densities as high as 2,500 mW/cm^2 with no apparent ill effects.

Chou and Galambos (1979) investigated effects in 10 guinea pigs of external-ear blocking, middle-ear damping, and middle-ear destruction on brainstem-evoked responses (BERs) to both acoustic and RFR stimuli. The basic measurement technique was to record the amplitudes and latencies of the BERs to acoustic stimuli and to RFR pulses with a pair of carbon-loaded Teflon electrodes, one of which was attached to the left mastoid process and the other to the skin. The results showed strong evidence that activation of the cochlea is necessary for auditory perception of pulsed RFR and that perception is due to transduction into acoustic waves that travel via bone conduction to the cochlea or are generated directly in the cochlea itself.

Tyazhelov et al. (1979) studied the qualities of apparent sounds perceived by humans from exposure to 800-MHz pulsed RFR. The parietal area of the head was exposed to the open end of a waveguide fed from a 500-W source. Pulse durations ranged from 5 to 150 μs. The pulses were presented either continuously at 50 to 2,000 pps (the latter for short pulse durations, to limit average power density) or in trains of duration 0.1 to 0.5 seconds at rates of 0.2 to 2.0 trains per second. Each person could be presented with sinusoidal audiofrequency (AF) sound waves independently of, or concurrently with, the pulsed RFR, and each person could adjust the amplitude, frequency, and phase of the AF signal to match the timbre and loudness of the perceived RFR.

The high-frequency auditory limit (HFAL) of each subject for tones from 1 kHz upward was tested first. Three subjects had HFALs below 10 kHz and could not perceive 10-30 μs RFR pulses, results that were consonant with those of Cain and Rissman (1978). Of 15 subjects with HFALs above 10 kHz, only one could not perceive the RFR pulses.

All of the perceptive subjects noted that 10-30 μs pulses delivered at 1,000 to 12,000 pps at peak power densities exceeding 500 mW/cm^2 produced sound of polytonal character that seemed to originate in the head, and that the quality of the sound changed with increasing pulse repetition rate (PRR) in a complex manner. Loudness diminished sharply and the sound became more monotonal as the PRR was increased from 6,000 to 8,000 pps, but no more than three distinguishable tonal transitions occurred. Subjects with HFALs below 15 kHz were unable to distinguish between the sounds perceived from a 5,000-pps and a 10,000-pps signal, and subjects with more extended HFALs reported that the pitch for a 5,000-pps signal was higher than for a 10,000-pps signal.

The subjects were able to detect small (5%) shifts of PRR only in the 8,000-pps region; at lower PRRs, the subjects erred on 100% of tests to detect the direction of PRR change, indicating that increases of PRR were often perceived as decreases in frequency. For pulses of constant peak amplitude, loudness was perceived to: increase with duration from 5 to 50 μs, decrease from 70 to 100 μs, and increase again for 100 μs and upward. Such patterns of perception were exemplified by plots of threshold pulse power (normalized to the 10-kHz PRR threshold) versus PRR for a subject with a 14-kHz HFAL and another subject with a 17-kHz HFAL. The curves were roughly W-shaped, with a central relative maxima at about 8 kHz. A plot of mean threshold pulse power (normalized to the threshold at 50-μs pulse duration) was also presented for subjects unable to perceive sounds for pulses longer than 50 μs. This curve was also W-shaped, with a central relative maximum within the pulse range 100-120 μs.

When acoustic tones above 8 kHz were presented concurrently with 10- to 30-μs pulses at PRRs slightly above or below 8 kHz, the subjects reported hearing beat-frequency notes. Also, for a PRR of 800 pps, similar beat frequencies were perceived when the acoustic frequency was set slightly above or below harmonics of the PRR. Moreover, when the tone and PRR frequencies were matched and the subjects were allowed to vary the phase of the acoustic tone, cancellation of perception of the two stimuli could be achieved. By proper phasing, the subjects with HFALs below 15 kHz could also achieve perception cancellation between a 10-kHz acoustic signal and a 5-kHz train of pulses.

The authors also reported that the sensory characteristics (pitch and timbre) evoked by RFR pulses less than 50 μs in duration were perceived as well when subjects' heads were lowered into seawater, with loudness diminishing roughly in proportion to the immersion depth and vanishing entirely with total immersion. For pulses longer than 50 μs, even partial immersion resulted in loss of perception.

Olsen and Hammer (1981) studied a spherical brain-equivalent model 10 cm in diameter. The model was exposed to 1.10-GHz RFR from an open section of waveguide, either as single pulses of 4-kW peak power and duration that was varied or as bursts of three pulses with an adjustable interpulse interval. For a nominal 10-μs pulse, the SAR was 824 W/kg at the center of the sphere and 653 W/kg at the surface facing the source. A hydrophone was placed at the center of the model to detect thermoelastic waves.

Exposure of the spherical model to single 14-μs pulses yielded ringing for each pulse, with a fundamental frequency of about 16 kHz and a time constant of about 500 μs. A plot of hydrophone response versus pulse duration over a 10-60 μs range showed maximum responses for 20-μs pulses. Bursts of three pulses each at burst frequencies ranging from 10 to 30 kHz yielded higher amplitudes than single pulses, with maximum enhancement at 16 kHz.

Olsen and Lin (1981) performed similar studies of spherical brain-equivalent models 6, 10, and 14 cm in diameter exposed to 10-kW, 1.10-GHz single pulses and to three-pulse bursts from an open waveguide section. A plot of the peak hydrophone responses of the 6-cm sphere to bursts of 10-μs pulses versus burst frequency showed maximum response at 25.5 kHz. The

corresponding data for the 10-cm sphere were the same as in Olsen and Hammer (1981). The response of the 14-cm sphere to single pulses was ringing at a fundamental frequency slightly above 10 kHz, and was maximum for 35-μs pulses. The responses of that sphere to bursts of 35-μs pulses had a peak at 11.5 kHz. Plots of the experimentally determined fundamental resonant frequencies for the three models were on the curve of resonant frequency versus head radius derived from the thermoelastic theory for a homogeneous brain sphere with stress-free boundaries, thereby supporting that theory.

In summary, Frey and coworkers were first to study the auditory effect in the U.S., but their hypothesis the effect was due to direct brain stimulation by the RFR pulses was disproved by later studies. Among the latter were White (1963), who demonstrated that thermoelastic acoustic waves can be generated in various media by RFR. Foster and Finch (1974) confirmed White's findings in water, and proved that such acoustic waves are not generated in water at 4 ^{o}C, where its thermal expansion coefficient is zero. Olsen and Hammer (1981) and Olsen and Lin (1981) investigated RFR-pulse transduction in spherical brain-equivalent models of the head and obtained results that support the thermoelastic theory for a homogeneous brain sphere with stress-free boundaries.

Taylor and Ashleman (1974) demonstrated that the effect does not occur in cats whose cochleas are destroyed. Guy et al. (1975b) confirmed the latter results, as did Chou and Galambos (1979). Guy et al. (1975b) also studied the hearing effect in two volunteers, and found that their respective threshold peak energy densities for pulse perception were 40 and 135 $\mu J/cm^2$ per pulse irrespective of the pulse durations used. Cain and Rissman (1978), using 3.0-GHz pulsed RFR, determined peak-power-density thresholds in volunteers for various pulse durations. Tyazhelov et al. (1979), in studying the qualities of apparent sounds perceived by humans from exposure to 800-MHz pulsed RFR, showed that pulse perception as sound could be modulated by concurrent reception of acoustic tones, but they also obtained some puzzling results.

Thus, the preponderance of experimental results indicates that perception of RFR pulses as sound results from induction of thermoelastic waves in the head, rather than by direct brain stimulation by the RFR. It is also important to note that because individual pulses of specific characteristics can be perceived, it is not meaningful to calculate time-averaged power densities for two or more widely spaced pulses and thereby to cite such values as evidence that the effect is nonthermal in nature.

3.1.5 RFR SHOCK AND BURN

Although it was known that RFR can cause electric shock in the body or burns in tissue under certain circumstances, specific exposure limits had not been included in the 1982 ANSI guidelines for human exposure to RFR. However, such effects were considered in choosing the 300-kHz lower frequency limit of those guidelines. Also, the 1988 exposure guidelines of IRPA/INIRC included such limits, as do the SCC 28 (1991) guidelines, based on the following studies.

In Rogers (1981), a simple apparatus ("RF Burn Hazard Meter") was described to measure the RF currents passing through a human in shoes standing

on a ground plane. Part of the apparatus consisted of a brass tube excited by an RF source, with the source connected to the ground plane. When a subject touched the tube with a finger, a loop consisting of the source, tube, body of the subject, and ground plane was closed to form a single-turn primary of a current transformer. The rest of the apparatus was the transformer secondary winding and its connections via diode detectors, resistors, and capacitors to a dc current meter. Rogers used this apparatus to measure the current levels that yielded a barely perceptible sensation ("perception" current) and that caused discomfort ("let-go" or "hazard" current) for frequencies in the MF (0.3-3 MHz) and HF (3-30 MHz) bands.

The author indicated that the perception current and let-go current for contact with the tip of the forefinger were both about twice those for contact with the back of the forefinger, and were even higher for large-area contact with the palm. Results for 50 persons tested (with the back of the forefinger) showed a mean hazard threshold current of about 200 mA for the band 2-20 MHz. The paper was devoted primarily to possible shipboard hazards to humans from metallic structures in the vicinity of onboard radiating antennas. Included were measured and calculated data for various structures and distances.

Rogers (1981) concluded that many shipboard structures can be excited sufficiently by ship transmissions in the HF band to present RF burn hazards to personnel and that cranes can be potent sources of RF burn hazards. The author also noted that RF burn hazards are present on structures when irradiated at field strengths that are much lower than those permissible for human exposure.

Gandhi and Chatterjee (1982) calculated the short-circuit currents induced in metallic objects (a 2.44-m x 1.22-m metal roof, a 50-ft metal fence, a compact car, and a forklift truck) and in a human (height 1.75 m, mass 68 kg), when each object is in a vertically polarized electric field at frequencies in the range 10 kHz to 10 MHz, and with each object assumed to be isolated from ground by 5 cm of insulation. They then calculated the incident electric fields necessary to produce threshold-perception and let-go currents for a human in conductive finger contact with each object. The threshold-perception current was defined as the smallest current that produces a tingling or pricking sensation due to nerve stimulation. The authors noted that the sensation changes from tingling to internal heat at frequencies above about 100-200 kHz. Let-go current was defined as the maximum at which a human can still release an energized conductor with muscles directly stimulated by that current.

The authors used experimental data on human perception-threshold and let-go currents of Dalziel and Mansfield (1950), Dalziel and Lee (1969), and Rogers (1981) for their calculations. They reproduced those data as log-log plots of perception-threshold and let-go currents versus frequency. The perception-threshold current showed a linear rise from about 0.4 mA at 10 kHz to 14 mA at 150 kHz, with a slower rise to about 100 mA at 20 MHz. The let-go current also showed a linear rise, from 6.4 mA at 10 kHz to about 85 mA at 150 kHz, and a slower linear rise to about 200 mA at 20 MHz.

By using the capacitance-to-ground for each object and the ratio of its electrostatically coupled short-circuit current to the unperturbed vertical field measured at 60 Hz by Deno (1974) and Bracken (1976), the authors obtained the effective area (S) and height (h) of the object. They assumed that these values are reasonably valid in the range 10 kHz to 3 MHz because the fields are quasi-static for objects with largest dimensions much smaller than the free-space wavelength.

Log-log plots of the calculated values of the unperturbed electric field (E) necessary to create threshold-perception and let-go currents in a human in finger contact with each object were presented. For each object, the threshold-perception value of E was constant in the range approximately 10-100 kHz: about 250, 160, 80, and 20 V/m for the roof, fence, car, and truck, respectively. In the range 10 kHz to 10 MHz, the threshold-perception field for the car and truck did not substantially change but those for the roof and fence decreased respectively to about 35 and 20 V/m at 10 MHz. The plots of E for let-go current vs frequency were similar: the plateaus for the roof, fence, car, and truck in the range 10-100 kHz were about 1040, 850, 440, and 110 V/m, respectively, with diminution for the roof and fence to less than 100 V/m at 10 MHz and smaller decreases for the car and truck.

The authors noted that based on an equivalent circuit of a human in conductive contact with an ungrounded, metallic object in a quasi-static HF field, there may be situations where the thresholds of perception and let-go can be exceeded for fields much lower than the ANSI guideline of 615 [sic] V/m, the far-field equivalent E-field associated with a power density of 100 mW/sq cm in the frequency band 0.3-3.0 MHz. They also noted that the effects will not occur if the conducting objects are grounded or insulated at the points of possible contact.

Chatterjee et al. (1986) measured the complex impedance (magnitude and phase) of the body and the threshold currents for perception and pain for 197 men and 170 women of ages between 18 and 70 years for the frequency range 10 kHz to 3 MHz. They defined the threshold-perception current for pain as the smallest current for which the subject reported "very uncomfortable sensations (similar to but more intense than that for perception) for which he/she will definitely not continue to touch the electrode any more."

Data on mean body impedance vs frequency for barefoot subjects standing on a ground plane and grasping a brass-rod electrode that was insulated from the ground plane were shown separately for men and women. Both the magnitude and the phase decreased monotonically with frequency, but the magnitudes for women was significantly higher than for men at corresponding frequencies. At 10 kHz, for example, the mean values for women and men were respectively about 630 and 520 ohms. The difference in mean phase at each frequency was not significant. Results for the subjects when using a saline-moistened index finger to touch a metal-plate electrode insulated from ground plane were similar, but of much higher magnitudes, respectively about 1900 and 1700 ohms at 10 kHz.

For men, the mean threshold-perception currents for finger contact rose linearly with frequency from about 4 mA at 10 kHz to about 40 mA at 100 kHz and remained at the latter value from 100 kHz to 3 MHz. The curve for

women was parallel to the curve for men, but was about 25% lower, a highly significant difference. Results for grasping contact were similar. The curves of finger-contact threshold currents for pain vs frequency also increased roughly linearly to maxima at about 100 kHz, but in the range 100 kHz to 3 MHz, diminished slightly with frequency. At 10 kHz, the mean pain-threshold currents for the men and women were respectively 10 and 6.5 mA, but their maxima at 100 kHz were nearly the same, about 14.5 mA. The authors indicated that the threshold-current values for 10-year-old children can be obtained from those for male adults by using a scaling factor of about 60%.

The sensation reported by the 367 men and women for frequencies below 100 kHz was tingling or pricking, localized in the area adjacent to the region of contact on the finger or hand; for frequencies above 100 kHz and finger contact with the plate electrode, the sensation was warmth or heat in the area below and around the plate electrode; with grasping contact, warmth or heat was felt in the hand and wrist. To determine more accurately the frequency for transition from tingling to warmth, data were obtained for some subjects at 50 and 70 kHz. At 50 kHz, the sensation reported was always tingling, but at 70 kHz, some subjects reported tingling and others warmth. When the current was raised slightly for those who reported tingling, the sensation changed to warmth. In addition, for frequencies above 100 kHz at which warmth was felt, when the current was adjusted to be equal to the perception threshold, pain was reported typically within 10-20 seconds, an effect that was not observed for frequencies below 100 kHz.

Chatterjee et al. (1986), at AM broadcast stations and at Coast Guard and Navy communication antenna sites in Hawaii, also determined: the short-circuit currents induced in humans while barefoot or wearing safety, leather-soled, or rubber-soled street shoes; the short-circuit currents induced in various vehicles; and the currents induced in humans in contact with these vehicles. Among the findings were that electrical safety shoes and gloves respectively provide protection that is adequate only at frequencies less than about 1 and 3 MHz. The measurements of induced short-circuit current showed reductions to 55% of the barefoot values with rubber-soled shoes, 63% with safety shoes, and 85% with leather-soled shoes.

The mean body impedances and threshold-perception currents were used to calculate the E-fields for threshold perception by grounded humans in finger contact with a compact car, van, and school bus. The results for adult males and 10-year-old children were plotted versus frequency in one set of graphs, and for adult females in another set. Similar sets of curves were obtained for threshold-perception E-fields with grasping contact. Also presented were similar sets of curves of the threshold E-fields for pain vs frequency for finger contact with such vehicles.

The threshold-perception curves for finger contact by men, women, and children were all entirely below 632 V/m, the 1982 ANSI limit for the range 0.3-3.0 MHz; the peaks at 100 kHz were in ascending order respectively for the school bus, van, and compact car. (The curves for the bus and van crossed at frequencies above 100 kHz.) Thus, currents from all three vehicles could be sensed at fields smaller than those recommended by ANSI for the range 0.3-3.0 MHz. For grasping contact, the school-bus threshold-perception curves for all three groups were also below the ANSI value over the entire frequency range;

those for the other vehicles were below that level except within frequency ranges of various sizes encompassing their respective peaks at 100 kHz.

The curves of pain-threshold E-field for finger contact with each type of vehicle were entirely below 632 V/m except for the curve for men in contact with the compact car. That curve exceeded 632 V/m in the range approximately 10-80 kHz, with a maximum of about 850 V/m at 30 kHz. All the other curves also had broader maxima at frequencies less than 100 kHz than those at 100 kHz for threshold perception.

The authors had measured the capacitance-to-ground of a GMC van that was well insulated from ground at a local AM broadcasting station operating at 700 kHz. The result was 1045 pf, which they used in a calculation of the current through the hand of a grounded human in conductive contact with the handle of such a van within a 3-MHz, 632-V/m field and obtained 879 mA. Based on this result and on an effective cross-sectional area of 11.1 sq cm for the wrist, they estimated that the corresponding local SAR in the wrist would be about 1045 W/kg.

The results of this study were presented in considerably greater detail in a final report by Gandhi et al. (1985a) and were published in Gandhi et al. (1985b). In Appendix B of that report were formulas for calculating local SARs in cross sections of the human leg (ankles, just below and above the knee, and two other thigh locations) for a human (barefoot and with safety shoes) immersed in a vertical field at the 1982 ANSI levels for the range 0.3-30 MHz. Calculations based on the assumption that half the body current flows through each leg indicated that SARs as high as 182 W/kg could occur in the ankle region.

Guy and Chou (1985) did an extensive study on possible hazards to humans from exposure to fields in the VLF-MF (10 kHz to 3 MHz) range, directed principally toward quantitation of thresholds and establishment of safety standards against such hazards. They noted that though SAR is generally used to quantify internal energy absorption, other quantities may be more important in the VLF-MF band for this purpose, because the amounts of energy absorbed by humans exposed to fields in that frequency range are relatively low but can cause direct neuromuscular effects from electric shock, and local tissue damage may result from electric contact between the subject and metallic objects in the field. In addition to SAR, important quantities include total electric current, I, in the body resulting from exposure while in contact with objects or surfaces in free space, and current density, J, through various body cross sections. Vast quantities of experimental and calculated data were presented.

The authors also noted that maximum energy coupling occurs when the longest dimension of the body is parallel to the electric vector, and that for exposure in this orientation to plane waves and most VLF-MF antenna sources, absorption from the magnetic component is more than an order of magnitude smaller than absorption from the electric component, so any restrictions on electric-field exposure will ensure restrictions on the corresponding magnetic fields that are more conservative by at least a factor of ten.

Guy and Chou (1985) also presented measurements of human exposures at the following sites to the frequencies indicated:

10.2 kHz	Haiku, HI
23.4 kHz	Lualualei, HI
24.8 kHz	Jim Creek, WA
146 kHz	Lualualei, HI
1 MHz	KOMO Radio, Vashon Island, WA

An important finding was that the highest local SARs occur in the ankles of the subjects, a result also found by Gandhi et al. (1985a). In the rationale of the 1982 ANSI guidelines, exposures at maximum local spatial SARs as high as 8 W/kg (averaged over any one gram of tissue and over any 0.1-hr period) would be permitted if the whole-body-averaged SAR does not exceed 0.4 W/kg. Guy and Chou (1985) noted that exposure to fields in the VLF-MF range would have to be restricted to 97 V/m to avoid exceeding the 8-W/kg limit.

3.2 MUTAGENESIS, CYTOGENETIC EFFECTS, AND CARCINOGENESIS

Mutagenesis and carcinogenesis are considered to be related, and many chemicals are screened for potential cancer-causing properties by testing whether such chemicals produce mutations in specific bacteria. RFR-induced mutagenic effects were sought in various plants and animals. Relatively few studies were done to determine whether RFR per se (e.g. 3 GHz) induces or promotes cancer. On the other hand, a few controversial epidemiologic studies have reported a statistical association of cancer promotion with exposure to powerline fields (60 Hz). Some have wrongly inferred that such findings are applicable to RFR exposure, a subject that is discussed more fully later.

3.2.1 MICROORGANISMS AND FRUIT FLIES

Various strains of Escherichia coli (E. coli) bacteria, Salmonella, or yeast are often used for seeking mutagenic and cytogenetic effects because cultures thereof can be grown under well controlled conditions and examined for the effects of various agents on growth, survival rates, and genetic changes. The fruit fly is also commonly used for mutagenesis investigations.

Blackman et al. (1976) sought possible mutagenic effects of RFR in a strain of E. coli in which mutations can be detected readily. Cultures were held at constant temperature while exposed to either 1.7 GHz at 2 mW/cm^2 (3 W/kg) or 2.45-GHz RFR at 10 or 50 mW/cm^2 (15 or 70 W/kg) for 3 to 4 hours. No significant differences in genetic activity were found between cultures exposed to either frequency for less than 3.2 hours and sham-exposed cultures.

Dutta et al. (1979) got similar results with Salmonella cultures exposed to 2.45-GHz RFR at 20 mW/cm^2 (40 W/kg).

Anderstam et al. (1983) investigated whether RFR is mutagenic for E. coli or Salmonella bacteria (using a total of 11 strains). The RFR frequencies, 27.12 MHz and 2.45 GHz, were selected because of their wide use in industry. For some RFR treatments, some strains showed higher growth and others lower growth than their respective controls. Many of the changes were statistically nonsignificant, but the overall trend was toward RFR-induced

increase in growth. Other results were both increases and decreases in mutant counts relative to controls, but most differences were nonsignificant.

In a study with the fruit fly, Pay et al. (1972) exposed male flies for 45 minutes to 2.45-GHz RFR at 6 mW/cm^2. Within 30 minutes after exposure, each male was placed in a vial with two virgin females. After initial mating, each male was placed in a new vial with two new virgin females every 24 hours for 15 days after exposure. On day 8 after each mating, the females were removed and the number of days to the emergence of the first adult flies in each brood was recorded as the generation time. All broods were counted on day 17 of growth. There were no significant differences between the exposed and control groups in mean generation times or brood sizes.

Hamnerius et al. (1979) exposed embryos of the fruit fly to 2.45-GHz amplitude-modulated RFR. The embryos were of a sex-linked, genetically unstable stock in which the eye color is light yellow. The mutation sought was somatic, in which a shift in eye pigmentation results in eye sectors with normal red pigmentation clearly visible against the yellow background, a mutation that occurs at an early stage of eye development.

For exposure, embryos were immersed in 10 ml of water within a Teflon container, which was placed inside a larger Plexiglas container through which flowed water held at 24.5 ^{o}C. The larger container was placed at about the start of the far-field region of a horn, at which site the RFR level was measured with a power-density meter. SAR was calibrated by measuring the temperature rise in a biological sample due to a 30-second exposure at 900 mW/cm^2 with no water flowing through the larger container; the result was 0.5 W/kg per mW/cm^2.

Embryo exposures were at 100 W/kg (about 200 mW/cm^2) for 6 hours. Controls were embryos similarly treated except for exposure. Following treatment, the embryos were transferred to vials that contained standard medium and were maintained at 25 ^{o}C and 75% relative humidity. The survival rate of the flies was determined from the number of male flies hatching from treated embryos, and the percentage of flies having red sectors constituted the mutation frequency. The mean survival rates for exposed and control flies were respectively 83% and 91%, a difference that was statistically nonsignificant. There were 4 mutations in 7,512 RFR-exposed males (0.05%) and 2 mutations in 3,344 control males (0.06%), also a nonsignificant difference.

Those authors also exposed fly embryos to X-rays as a positive control, and found that 1,000 rad yielded 29 mutations in 1,053 males (2.75%). This result led them to conclude that with a sample size of 7,512 males, it would be possible to detect this mutagenic effect at 50 rad ($p=0.05$). The authors also noted that the chemical mutagen EMS yielded 444 mutations in 4,859 males (9.14%) at 9.75 mM, but they made no further comparison.

Confounding parameters, especially temperature rise, appear to have been controlled adequately, so the finding of no RFR-induced mutagenic effect in this study is highly credible.

In summary, Blackman et al. (1976) found no significant differences in genetic activity in cultures of a strain of E. coli in which mutations can be

detected readily when such cultures were exposed to either 1.7 GHz at 2 mW/cm^2 (3 W/kg) or 2.45-GHz RFR at 10 or 50 mW/cm^2 (15 or 70 W/kg). for 3 to 4 hours with temperature held constant. Dutta et al. (1979) got similar results with Salmonella cultures exposed to 2.45-GHz RFR at 20 mW/cm^2 (40 W/kg). Because of their wide use in industry, Anderstam et al. (1983) selected 27.12 MHz and 2.45 GHz to determine whether such RFR is mutagenic for E. coli or Salmonella bacteria (using a total of 11 strains). Both increases and decreases in mutant counts relative to controls were seen, but most differences were nonsignificant.

The study by Pay et al. (1972) involving exposure of male fruit flies for 45 minutes to 2.45-GHz RFR at 6 mW/cm^2 and subsequent matings with female fruit flies showed no significant differences between exposed and control groups in mean generation times or brood sizes. Hamnerius et al. (1979) had exposed fruit fly embryos from a sex-linked, genetically unstable stock having light-yellow eyes instead of red eyes to 2.45-GHz RFR at 100 W/kg (about 200 mW/cm^2) for 6 hours. Only 4 mutations in 7,512 RFR-exposed males (0.05%) and 2 mutations in 3,344 control males (0.06%) were seen, a nonsignificant difference. The authors also exposed fly embryos to X-rays as a positive control, and found that 1,000 rad yielded 29 mutations in 1,053 males (2.75%). They also noted that the chemical mutagen EMS yielded 444 mutations in 4,859 males (9.14%). Thus, there is no evidence that exposure to RFR induces mutations in bacteria, yeasts, or fruit flies.

3.2.2 MAMMALS AND MAMMALIAN TISSUES

Skidmore and Baum (1974) sought biological effects of exposure to "EMP" (electromagnetic pulses resembling the RFR from a nuclear blast). They exposed five pregnant rats to a peak electric field of 447 kV/m in an EMP simulator during 17 days of gestation, a total of about 7 million pulses, with five unexposed pregnant rats as controls. On completion of exposure, the fetuses were examined for gross abnormalities. None were found. Twenty female rats were exposed almost continuously to the EMP for 38 weeks (about 100 million pulses) and were observed for possible development of mammary tumors, together with 20 controls. At age one year, no mammary tumors were found in either group.

Those authors also exposed 50 male mice of strain AKR/J, known to be susceptible to spontaneous leukemia development between 6 and 12 months of age, to the EMP. After 33 weeks of exposure (86 million pulses), 42 (84%) of the EMP-exposed mice and 24 (48%) of the unexposed control mice survived and were examined for leukemia. It could be inferred from those results that exposure to the EMP was beneficial. On the other hand, not clear is why almost half of the control mice died.

Of the survivors, 9 exposed mice (21%) and 11 control mice (46%) were leukemic, a nonsignificant difference. However, the sample sizes were too small to ascribe much if any validity to the latter finding.

The authors also sought possible effects of the EMP on fertility by exposing five 4-month-old male/female pairs of rats for 13 weeks. The males were separated from their partners for the first 8 days, but housed with their mates for the remainder of the period. Five unexposed pairs of rats were

treated similarly. The numbers of progeny were recorded at term and each neonate was examined for anatomical abnormalities. Also sought were effects of exposure on the fertility of five 2-year-old male rats by mating them on exposure termination with unexposed 4-month-old females. No anatomical abnormalities were found and there were no significant differences in numbers of progeny.

Varma and Traboulay (1976) exposed the testes of 10 anesthetized 56-day-old mice to 1.7-GHz CW RFR at 50 mW/cm^2 for 30 minutes and the testes of 10 other mice at 10 mW/cm^2 for 80 minutes. Ten mice were sham-exposed with each RFR group. After 24 hours for recovery, each mouse was caged for one week with three 56-day-old unexposed virgin females, and each subsequent week with new virgin females for 7 weeks. The authors used the "dominant lethal test" (mutations that result in death of the embryo) to assess whether either RFR level was mutagenic. On gestation day 13, the females were euthanized and the numbers of live implants, late fetal deaths, and resorption sites were used to calculate the ratio of number of early fetal deaths to total number of implants.

The data contained tabulation errors and the statistical calculation was done incorrectly. With appropriate corrections, the differences in overall values between the RFR and sham groups were significant for both exposure conditions, but nonsignificant for most of the individual weeks postexposure. Exposure of the testes at 50 mW/cm^2 for 30 minutes caused a marked reduction in fertility, but exposure at 10 mW/cm^2 for 80 minutes caused only a marginal reduction.

As noted above, the mice were anesthetized during exposure. Only the testes were exposed, while their bodies were shielded from the RFR. However, anesthesia markedly reduces the ability of rodents to control their body temperature. Thus, the exposures may have caused substantial rises in testicular temperature, so the results may not represent those for unanesthetized mice exposed to RFR at the same levels for the same durations.

Berman et al. (1980) conducted experiments on male fertility in rats by breeding RFR-exposed males with unexposed females. No evidence was found for an increase of dominant lethal mutations from 2.45-GHz RFR at power densities up to 28 mW/cm^2 (5.6 W/kg). Regarding male fertility, the authors noted that only under the most severe exposure regimen was there any hint of a deleterious effect: Only 50% of the females bred to the exposed males 3-9 days after treatment became pregnant. Presumably, this temporary sterility was associated with the rises in rectal and intratesticular temperatures measured during exposure.

McRee et al. (1981), noting that analysis of induction of sister chromatid exchange (SCE) is a sensitive technique for assaying genetic damage from mutagens and carcinogens, used the technique to determine whether RFR is mutagenic in mice. They exposed 12 10-week-old mice 8 hours per day for 28 days to 2.45-GHz RFR at 20 mW/cm^2 (about 27 W/kg), with two other groups as controls. After exposure completion, the SCEs in bone marrow were determined and the mitotic index for bone marrow cells was scored. The results for the three groups were comparable, an indication that there were no statistically

significant effects of the RFR on SCEs or the proliferation rate of bone-marrow cells.

Meltz et al. (1990) investigated whether pulsed 2.45-GHz RFR alone can induce mutagenesis, chromosal aberrations, and SCEs in mammalian cells, and whether the RFR can alter the genotoxic damage induced by a chemical mutagen alone when the RFR is administered simultaneously with the mutagen. The chemical agent used was proflavin, a DNA-intercalating drug (able to insert additional nucleotide bases into DNA sequences), and the mammalian cells studied were derived from a mouse leukemic cell line and purified of spontaneous mutations.

The six treatments listed below were conducted simultaneously on appropriately prepared and diluted cell samples in petri dishes, with each treatment involving two or four replicate, independent-treatment dishes, and with all treatments administered for 4 hours in the dark. A sample treated with ethylmethane sulfonate (EMS) was run as a positive control for each set of replicates.

(1) Controls at 37 ^{o}C (no RFR and no proflavin).

(2) RFR exposure alone, with no temperature control.

(3) RFR exposure with temperature control (heat convection to yield a temperature rise closely following that with RFR alone).

(4) Proflavin treatment alone, at 37 ^{o}C.

(5) Proflavin treatment with simultaneous RFR.

(6) Proflavin treatment with simultaneous temperature control.

The RFR exposures were to 10-μs, 2.45-GHz pulses at 25,000 pps (0.25 duty factor) in an anechoic chamber. The average power densities at the sample plane were 87 mW/cm^2 in the first two RFR experiments and 65 mW/cm^2 in the third RFR experiment. The corresponding SARs were 40.8 and 40.0 W/kg, respectively.

The combined RFR and proflavin treatment yielded no statistically significant increase in induced mutant frequency relative to the results for treatment with proflavin alone. Also, exposure to RFR alone yielded no evidence of mutagenic action.

In summary, the study by Skidmore and Baum (1974) seeking biological effects of EMP yielded negative findings: Exposure of five pregnant rats to a peak electric field of 447 kV/m in an EMP simulator during gestation (a total of about 7 million pulses) produced no gross abnormalities in the fetuses. Exposure of 20 female rats almost continuously to the EMP for 38 weeks (about 100 million pulses) produced had no mammary tumors at age one year. Exposure for 33 weeks (86 million pulses) of 50 male mice of a strain susceptible to the spontaneous leukemia development yielded 42 (84%) survivors but only 24 (48%) survivors in 50 unexposed control mice. Those percentages appear to indicate that the exposure to the EMP was beneficial. Examination of the

survivors showed that 9 exposed (21%) and 11 control (46%) mice were leukemic, a nonsignificant difference, but the latter sample sizes were too small to ascribe any validity to that finding. The authors, on mating EMP-exposed males with virgin females, also found no significant differences in the numbers of progeny and no anatomical abnormalities in the neonates.

The study by Varma and Traboulay (1976) showed that exposure of male rodents to RFR levels that produce frank heating of the testes (10-50 W/kg) tend to reduce fertility, but that such levels were not mutagenic as determined by the dominant lethal test. The experiments on male fertility in rats by Berman et al. (1980) yielded no evidence of an increase of dominant lethal mutations from 2.45-GHz RFR at power densities up to 28 mW/cm^2 (5.6 W/kg).

McRee et al. (1981) found no statistically significant effects of exposure of mice to 2.45-GHz RFR at 20 mW/cm^2 (about 27 W/kg) on the induction of sister chromatid exchanges (SCEs), a sensitive technique for assaying genetic damage from mutagens and carcinogens, or on the rate of proliferation of bone-marrow cells.

The study by Meltz et al. (1990) on exposure of cell cultures from a mouse leukemic cell line to pulsed 2.45-GHz RFR at about 40 W/kg, either alone or in combination with the chemical mutagen proflavin, yielded negative findings: The RFR in combination with proflavin produced no statistically significant increase in induced mutant frequency relative to the results for treatment with proflavin alone. Also, RFR exposure alone yielded no evidence of mutagenic action.

3.2.3 CANCER INDUCTION AND PROMOTION IN ANIMALS

Possible association between chronic RFR exposure and incidence of cancer has been reported in some epidemiologic studies (see Section 3.1.1), but for the reasons stated therein, little credence can be given to such findings. On the other hand, few studies specifically directed toward determining whether RFR induces or promotes cancer in animals have been performed.

Prausnitz and Susskind (1962) exposed 200 mice to 9.3-GHz pulsed RFR for 4.5 minutes per day, 5 days per week, for 59 weeks at an average power density of 100 mW/cm^2 (45 W/kg estimated SAR), with 200 other mice as controls. An unexpected finding was the development of leukosis in some of the mice, with incidence greater in the exposed mice than in the control mice. The authors mistakenly described leukosis as a "cancer of the white blood cells," thereby implying a link between RFR exposure and cancer incidence. In actuality, however, leukosis is defined basically as elevation of the numbers of circulating leukocytes, which in this study may have been due to the known occurrence of infection in the mouse colony, or to other functional disturbances.

Roberts and Michaelson (1983), in a reanalysis of the primary data of Prausnitz and Susskind (1962), concluded that this study provided no evidence that chronic RFR exposure does or does not induce any form of cancer.

As previously discussed in Section 3.2.2, Skidmore and Baum (1974) found that continuous exposure of 20 females to EMP did not lead to the development of any mammary tumors, and that EMP exposure of mice of the AKR/J strain prone to spontaneous leukemia did not promote leukemia; 21% of exposed mice versus 46% of control mice developed leukemia.

Szmigielski et al. (1982) sought to determine whether RFR would alter the incidence of breast tumors in mice of strain C_3H/HeA known to have high spontaneous incidence of such tumors. Female mice were exposed in four groups of 10 mice each at a time to 2.45-GHz RFR at 5 mW/cm^2 (SAR 2-3 W/kg) or 15 mW/cm^2 (6-8 W/kg). Each group of 10 mice was purposely confined in a polymethacrylate cage, a condition known to be stressful to the mice. The exposures were for 2 hours a day, 6 days a week, for 1 to 6 months, starting at age 6 weeks and ending at 12 months. Temperature (22-23 ^oC) and humidity (60-70%) within the exposure chamber were said to have been held stable by external ventilation. Three other sets of 40 mice were respectively sham-exposed, raised under chronic confinement stress, and maintained as cage controls. The mice were checked every two weeks for appearance of palpable breast tumors.

The cumulative numbers of mice with discernible tumors and their survival times were tabulated, and the results were summarized in terms of CDT_{50} (mean cancer development time in 50% of the mice) and MST_{50} (mean survival time of 50% of the mice). The CDT_{50} was 219 days for 15 mW/cm^2, 261 days for 5 mW/cm^2, 255 for confinement-stressed mice, and 322 days for cage controls. Thus, the results for 5 mW/cm^2 and confinement stress were comparable and were between those for 15 mW/cm^2 and the cage controls. The results for MST_{50} were analogous.

At 5 mW/cm^2 (2-3 W/kg), no increase in rectal temperature was seen, but the authors noted that such SARs exceed the basal metabolic rate of the mice; no rectal-temperature increase was seen at 15 mW/cm^2 (6-8 W/kg) either, but the authors suggested the possible existence of "hot spots" within the mice. At the higher level, the RFR must have increased the stress on the mice considerably. Since confinement stress alone was shown to increase tumor incidence, it seems likely that the heat stress from the RFR was responsible for the increases in tumor incidence, rather than a postulated existence of intrinsic carcinogenic properties of RFR.

The authors also investigated whether RFR increases the incidence of skin cancer in Balb/c mice caused by the known carcinogen 3,4-benzopyrene (BP) painted on the depilated skin. To evaluate the effects of BP alone, 40 six-week-old male Balb/c mice were painted with BP (in a solvent) every other day for 5 months; controls were similarly painted only with the solvent. Cancer development was scored on a subjective scale of 0 to 6 by histopathologic examination. At a score of 4, small papillomas were found microscopically to contain cancer cells, so mice with scores of 4-6 were regarded as having skin cancer and those with scores 1-3 as having precancerous skin lesions.

The CDT_{50} values for skin-cancer appearance in Balb/c mice were 131, 208, 235, and 296 days respectively for 15 mW/cm^2, confinement stress, 5 mW/cm^2, and BP-painted controls. Thus, the value for confinement stress was somewhat higher than for 5 mW/cm^2, and both were between the values for 15

mW/cm^2 and BP-painted controls, results that were similar to those for breast tumor in the C_3H/HeA mice. Again, the RFR-induced increases in skin-cancer incidence were probably due to the heat stress rather than any postulated intrinsic carcinogenic properties of the RFR.

In a University of Washington study of chronic exposure, discussed in nine reports [Chou et al. (1983), Guy et al. (1983a, 1983b, 1985), Johnson et al. (1983, 1984), Kunz et al. (1983, 1984, 1985)], 100 male rats were exposed unrestrained within individual cylindrical waveguides to 2.45-GHz RFR at average power densities of about 0.5 mW/cm^2 under controlled-environmental and specific-pathogen-free conditions. The exposure levels were selected to simulate, by scaling considerations, chronic exposure of humans to 450-MHz RFR at SARs about 0.4 W/kg (the basis of the 1982 ANSI guidelines). The rats were exposed for virtually their entire lifetimes, except for those withdrawn for interim tests. One hundred sham-exposed male rats comprised the controls.

The exposure regimen was begun when the rats were 8 weeks old and was continued for 25 months, which, except for the rats withdrawn for interim tests, encompassed virtually their entire lifetimes. After 13 months, 10 each of the RFR- and sham-exposed rats were euthanized (the interim kill), as were 10 of the 12 RFR-exposed and 10 of the 11 sham-exposed rats that survived to the end of the 25-month exposure regimen.

No significant differences between groups were seen in daily body weight, food and water consumption, oxygen consumption, carbon dioxide production, or respiratory quotient at corresponding times. At each kill, the hearts, brains, livers, kidneys, testicles, and adrenals of the RFR- and sham-exposed rats were weighed, and the composition, fatty acid profile, and mineral content of the carcasses were analyzed. At interim kill, no significant differences between groups were seen in the mass of any organ. At terminal kill, mean adrenal mass for the RFR group was 75% higher than for the sham group, but the differences for the other organs were not significant.

During the exposure regimen, 157 rats had died spontaneously or were terminated *in extremis*. (Of the remaining 43 rats, 20 rats comprised the interim-kill groups; the other 23 were the survivors at the end of the exposure regimen and comprised the terminal-kill groups). Evaluation of the cumulative survival curves showed that the median survival times for the RFR- and sham-exposed rats were respectively 688 and 663 days, but comparison of the curves by the log-rank statistic showed no significant difference between the groups at any age. The authors remarked that no significant infections had occurred to complicate or produce erroneous results in gross or histopathological evaluations.

Various immunologic and hematologic tests were done, the results of which are described in Section 3.5.3.

In 20 rats necropsied at the interim kill, no adrenal tumors were found, but 7 of the 12 RFR-exposed rats and 4 of the 11 sham-exposed rats necropsied at the terminal kill were found to have benign adrenal tumors. The authors related the higher adrenal mass to the tumors. Exclusion of the rats with adrenal tumors from both groups rendered the difference in mean adrenal mass nonsignificant.

Gross and histopathological examinations were done. Primary causes of death (31 specific causes, 1 unknown-cause category, and the 2 kills) were tabulated separately for the RFR and sham groups. The numbers of deaths for most causes were small, so the table was collapsed into four specific major causes (defined as having at least 5 deaths), plus the "kills" category and a category that comprised all other causes.

Kidney failure (glomerulonephritis) was the largest cause, with 17 deaths in the RFR group and 15 in the sham group; next was urinary tract blockage, with 9 and 19 deaths in the RFR and sham groups, respectively; third was atrial thrombosis, with 7 and 9 deaths; fourth was pituitary adenoma, with 4 and 8 deaths.

There were 22 RFR-exposed and 21 sham-exposed rats in the two kill groups. The all-other category had 41 deaths in the RFR group and 28 in the sham group. Chi-square analysis showed no association between cause of death and exposure condition. Also, the log-rank statistic showed no significant differences between the RFR and sham groups in the survival times for glomerulonephritis, atrial thrombosis, or pituitary adenoma; the RFR group had significantly longer survival times for urinary tract blockage than the sham group.

The lesions found in the various organs and tissues during necropsy were characterized as non-neoplastic or neoplastic, and the neoplastic lesions were subdivided into benign and malignant. Of the non-neoplastic lesions, glomerulonephropathy was the most prevalent. Analysis of the data by incidence, age, and treatment indicated that significantly fewer glomerulonephropathic lesions had occurred in the RFR group. There were no significant differences between the RFR and sham groups for nine other major types of non-neoplastic lesions.

Only 3 benign neoplasms occurred in rats younger than 1 year, and those were in the sham group. During the second year, benign neoplasm incidence rose rapidly with age for both the RFR and sham groups, but the differences between groups at each age of death were nonsignificant.

No primary malignant lesions were found in the rats younger than 1 year. Primary malignant lesions were found in 2 RFR-exposed and 2 sham-exposed rats at ages 13-18 months, in 9 of the RFR group and 1 of the sham group at ages 19-24 months, and in 7 of the RFR group and 2 of the sham group at ages 26-30 months. Totals without regard to age were 18 for the RFR group and 5 for the sham group.

The authors gave little credence to the higher total number of rats affected in the RFR group than in the sham group, because the differences in numbers for each specific malignancy type were all nonsignificant and statistical significance was attained only by combining the sparse data for each type of malignancy. Moreover, the incidence of each specific primary malignancy in the RFR group was similar to that in the literature for untreated rats of the same strain. The investigators also noted that from the standpoint of carcinogenesis, benign neoplasms have considerable significance under the assumption that the initiation process is similar for both benign

and malignant tumors. The fact that the RFR and sham groups showed no difference in the incidence of benign tumors is an important element in defining the promotion and induction potential of RFR for carcinogenesis.

Others have claimed that all of those malignancies can be grouped together as "tumors of the endocrine system," a classification that is not recognized as valid by most members of the toxicology community.

The investigators stated: "In summary, no defendable trends in altered longevity, cause of death, or spontaneous aging lesions and neoplasia can be identified in the rats exposed to this long-term low-level radiofrequency radiation exposure."

Santini et al. (1988) sought to determine whether low-level exposure of black mice (strain C57BL/6J) would have any effect on the development of B16 melanoma or survival times. The authors exposed one group of 15 mice to 2.45-GHz CW RFR at 1 mW/cm^2 (SAR 1.2 W/kg) for 6 daily sessions per week, each 2.5 hours a day, until death (up to 690 hours total). Another group was similarly exposed to 2.45-GHz pulsed RFR at the same average power density. A third group was sham-exposed as controls. No statistically significant differences were found among the three groups in either tumor development or survival.

Balcer-Kubiczek and Harrison (1991) studied whether exposure to RFR of mouse-embryo-fibroblast-cell cultures induces malignant transformation in such cells. They exposed such cultures for 24 hours to 2.45-GHz RFR (amplitude-modulated at 120 Hz) at an SAR of 0.1, 1, or 4.4 W/kg alone, or to the RFR at 4.4 W/kg before or after exposure to X-rays at 0.5, 1, or 1.5 Gy. Control cultures were sham-exposed. After such treatments, cultures with or without incubation with a known tumor promoter (TPA) were assayed for incidence of neoplastic transformations by counting the number of transformed foci in culture dishes.

The sham-exposed cultures exhibited low incidences of neoplastic transformation; those incubated with TPA showed a slightly higher mean incidence than those not incubated with TPA. A plot of mean neoplastic transformation incidence (linear scale) versus SAR (exponential scale) for the RFR-exposed cultures not incubated with TPA exhibited essentially no differences from sham-exposed cultures or any changes with increasing SAR, so the RFR alone did not promote transformation. However, the mean neoplastic transformation incidence rose with SAR for the RFR-exposed cultures incubated with TPA. The authors regarded those results as indicating that RFR acts synergistically in a dose-dependent manner with TPA to promote neoplastic transformation.

In graphs of mean neoplastic transformation incidence (linear scale) versus X-ray dose (linear scale, unlike that for SAR), the cultures not incubated with TPA showed a relatively small rise with X-ray dose (0, 0.5, 1.0, 1.5 Gy), essentially independent of RFR level (0 or 4.4 W/kg) or whether X-ray exposure preceded or followed RFR exposure. For the cultures incubated with TPA, however, the mean transformation incidence rose linearly with X-ray dose for the cultures exposed to 4.4 W/kg, and also linearly for the sham-

exposed cultures but with about half the mean incidences of the 4.4-W/kg cultures at corresponding X-ray doses.

There are several questionable points regarding this paper. First, the use of an exponential scale for SAR may be misleading. That plot shows an apparently linear rise of incidence with SAR (0.1, 1.0, 4.4 W/kg). However, if the points for the three SARs are plotted on a linear scale (as was done for the X-ray points), the graph would display a much sharper rise with SAR between 0.1 and 1.0 W/kg than between 1.0 and 4.4 W/kg: The slope for the line connecting the points for 0.1 and 1.0 W/kg was more than five times larger than for the line connecting the points for 1.0 to 4.4 W/kg. Those slope differences could be interpreted as indicating onset of saturation of the effect at the higher SARs, but the small numbers of foci per dish (discussed below) would rule that out.

An examination of Table I of the paper, in which the data for each treatment are summarized, reveals the more fundamental problem that the number of transformed foci counted in each dish was very small. The following are two representative examples. In addition, not mentioned in the paper was whether those who did the identification of foci had prior knowledge of the treatment of each dish.

a. Only 14 foci were found in 1494 dishes of sham-exposed cultures incubated with TPA, and only 4 foci were found in 887 dishes of sham-exposed cultures not incubated with TPA.

b. Only 48 foci were found in 704 dishes of cultures exposed at 4.4 W/kg incubated with TPA, and only 4 foci were found in dishes exposed at 4.4 W/kg not incubated with TPA.

It seems clear that the various statistically significant results presented in the paper were attained solely by adding very small counts (perhaps a few foci per dish in some dishes and none in others), a rather dubious process. Such small counts per dish could be regarded as being within the "noise level" for each experiment. Also, with such sparse populations of foci on each dish, missing one focus on one or more sham-exposed dishes or misidentifying a spot as a focus on one or more RFR-exposed dishes could greatly alter the results. A possible problem of this kind could be compounded if such counts are not done blind (without prior knowledge of the treatment of each dish).

There are also reports that electric and/or magnetic fields at powerline frequencies (e.g., 60 Hz) can promote cancer, a subject of considerable controversy. This subject was discussed in Section 2.5.

In summary, in the study by Prausnitz and Susskind (1962) involving exposure of 200 mice to 9.3-GHz pulsed RFR at 100 mW/cm^2 (about 45 W/kg) for 4.5 minutes per day, the authors had indicated occurrence of leukosis in both the exposed and control mice, but in more of the exposed than the control mice. The authors had mistakenly described leukosis as a "cancer of the white blood cells". However, leukosis is defined basically as an elevation of the numbers of circulating leukocytes, which in this study may have been due to the occurrence of an infection in the mouse colony reported by the authors, or

to other functional disturbances. Roberts and Michaelson (1983), in a subsequent reanalysis of the primary data, concluded that the Prausnitz and Susskind (1962) study provided no evidence that chronic RFR exposure does or does not induce cancer.

As previously discussed in Section 3.2.2, Skidmore and Baum (1974) had found that continuous exposure of 20 females to EMP did not lead to the development of any mammary tumors, and that EMP exposure of mice of the AKR/J strain prone to spontaneous leukemia did not promote leukemia; 21% of exposed mice versus 46% of control mice developed leukemia.

Szmigielski et al. (1982) had studied whether exposure of mice of a stain known to have high spontaneous incidence of breast tumors to 2.45-GHz RFR at 5 mW/cm^2 (SAR 2-3 W/kg) or 15 mW/cm^2 (6-8 W/kg) would alter the incidence of such tumors, measured by the mean time for palpable breast tumors to develop in 50% of the mice. Four groups of mice were purposely confined during RFR exposure to stress them, and one group each was sham-exposed, raised under chronic confinement stress without exposure to RFR, and maintained as cage controls.

The mean times for tumor development for the groups exposed at 5 mW/cm^2 and for those stressed by confinement were comparable, and were between the mean times for the groups exposed at 15 mW/cm^2 and the cage controls, a positive finding. However, because confinement stress alone was found to increase tumor incidence, it seems likely that the added heat stress by the higher RFR level was responsible for the increases in tumor incidence, and not from any postulated carcinogenic properties of RFR per se.

Szmigielski et al. (1982) had also similarly investigated whether the incidence of skin cancer in mice from painting a known carcinogen on the skin is increased by RFR exposure. Again, the RFR-induced increases in skin-cancer incidence were probably due to the heat stress at the higher RFR level rather than from any intrinsic carcinogenic properties of the RFR.

The overall findings of the chronic study by the University of Washington showed no significant differences between the RFR- and sham-exposed rats at periodic test sessions, but small numbers of various types of malignant lesions were found in both groups at the end of the exposure regimen. The numbers of rats that had each type of malignancy were similar to those reported in the literature for untreated rats of the same strain, and the differences in numbers for each specific malignancy were all statistically nonsignificant.

The study by Santini et al. (1988) on possible development of B16 melanoma or survival times in black mice from exposure to 2.45-GHz CW RFR at 1 mW/cm^2 (SAR 1.2 W/kg) yielded no significant differences in either tumor development or survival among the exposed, sham-exposed, and control groups.

Balcer-Kubiczek and Harrison (1991) had exposed cultures of mouse-embryo-fibroblast cells to induces malignant transformation in such cells to 2.45-GHz RFR 0.1, 1, or 4.4 W/kg alone, or to the RFR at 4.4 W/kg before or after exposure to X-rays at 0.5, 1, or 1.5 Gy. After such treatments, they incubated the cultures with or without incubation with a known tumor promoter

(TPA), and assayed them for incidence of neoplastic transformations by counting the transformed foci in each culture dish.

The results for RFR alone showed no evidence of tumor promotion. However, the mean neoplastic transformation incidence rose with SAR for the RFR-exposed cultures incubated with TPA, results that the authors regarded as indicating that RFR acts synergistically in a dose-dependent manner with TPA to promote neoplastic transformation. Little credence can be given the latter results because of the small numbers of foci per dish. For example, in the cultures exposed at 4.4 W/kg, only 48 foci were found in 704 dishes incubated with TPA and only 4 foci were found in dishes not incubated with TPA, but in the sham-exposed cultures there were 14 foci in 1,494 TPA-incubated cultures and 4 foci in 887 non-TPA-incubated exposed cultures. Thus, the statistically significant results presented in the paper were attained solely by adding very small counts. Also, apparently the counting was not done without prior knowledge of the treatment of each dish.

3.2.4 CONCLUSIONS

Collectively, the studies above provide no scientifically credible evidence that exposure of either mammalian or non-mammalian subjects to low levels of RFR produces mutations, cytogenetic effects, or that such RFR induces or promotes any form of cancer in mammals or cultures of mammalian cells.

3.3 TERATOGENESIS

Teratogenesis refers to the causation of anatomical aberrations in a developing fetus, but more generally also includes fetal death and/or resorption, and postnatal abnormalities in the offspring. Such effects occur naturally at low rates in most mammals, and relatively little is known about their causes. In a few cases, however, specific agents have been shown to cause significant effects, and hence the possibility that such effects could occur from exposure to RFR is an appropriate matter of public concern. The term is usually applied to mammalian fetuses and infants, but effects on nonmammalian subjects also have been sought.

3.3.1 NONMAMMALIAN SPECIES

Several investigations were done with pupae of the darkling beetle. Carpenter and Livstone (1971) exposed individual pupae to 10-GHz RFR for 2 hours at 17 mW/cm^2 (40 W/kg estimated SAR) or at 68 mW/cm^2 (160 W/kg) for 20 or 30 minutes. As representative results, only about 20% of the pupae exposed at the lower RFR level developed into normal beetles; about 4% died and 76% had gross abnormalities. Exposure for 20 minutes at the higher RFR level yielded about 24% normal beetles, 25% dead ones, and 51% with gross abnormalities. By contrast, 90% of the sham-exposed pupae developed normally. Also, about 75% of the pupae heated conventionally to the temperature obtained with 17 mW/cm^2 emerged as normal beetles, leading the authors to conclude that abnormal development of RFR-exposed pupae could not be explained as a thermal effect. Liu et al. (1975) exposed pupae for 2 hours to 9-GHz RFR at 0.17 mW/cm^2 (about 0.41 W/kg), which also yielded significant percentages of abnormal beetles.

On the other hand, Pickard and Olsen (1979) investigated pupae they had developed from larvae obtained from two sources (designated "colony-pupae" and "K-pupae"). Pupae from both groups were exposed for 2 hours to a 6-GHz standing-wave electric field or magnetic field with their long axes parallel to the vector. The E-field exposures were at 91 V/m (130 W/kg) and the H-field exposures were at 1.53 A/m (54 W/kg). Pupae were also exposed for 13 hours to far-field 6-GHz RFR at 11 mW/cm^2 (about 130 W/kg) and for 4 hours to far-field 10-GHz RFR at 5 mW/cm^2 (45 W/kg).

For either group given E-field exposure, the percentage of beetles with abnormalities did not differ significantly from that of its control group. However, the proportion of nonnormal beetles from control K-pupae was significantly higher than from control colony-pupae. Also, H-field exposure produced significant effects on K-pupae but not on colony-pupae. The exposures to the other forms of RFR yielded ambiguous results. The authors ascribed those variations to uncontrolled differences in such non-RFR factors as the source of the larvae, pupae maintenance regimes and handling protocols, the pupa containers used for pupation, and the ambient temperature.

Pickard and Olsen (1979) concluded that RFR could be teratogenic to the darkling beetle, but their results did not support the nonthermal hypothesis of Carpenter and Livstone (1971). In addition, Olsen and Hammer (1982) thermographically determined spatial distributions of SAR within pupae when exposed to 1.3-, 6-, and 10-GHz RFR, and found large variations of local SAR that would not be obtained by the conventional heating used by Carpenter and Livstone (1971).

In their studies of Japanese quail, McRee and coworkers found no significant differences between hatchlings from eggs exposed to 2.45-GHz RFR at a whole-egg SAR of 14 W/kg and sham-exposed eggs in average body weights, numbers and percentages of eggs hatched, numbers and percentages of hatched and unhatched live and dead birds, and blood parameters. In addition, no deformities were seen in the hatched quail. The authors concluded that RFR is not teratogenic except at hyperthermic levels.

The study by Gildersleeve et al. (1987) on reproductive performance of Japanese quail from eggs that had been exposed to 2.45-GHz RFR at 5 mW/cm^2 (4 W/kg) during the first 12 days of embryogenesis also showed that exposure to the RFR during embryogenesis did not affect any of the endpoints they studied, which included: hatchability, mortality after hatching, egg production, egg weight, fertility of the initial groups, and reproductive performance of the progeny.

3.3.2 MAMMALS

In some studies with mice, RFR exposure has been reported to cause various teratogenic effects, but negative or inconsistent results were obtained in others.

Rugh et al. (1974, 1975) exposed groups of female mice to 2.45-GHz RFR at 138 mW/cm^2 (SAR about 123 W/kg) for various durations to determine "D/M", the mean dose (power density x duration) per unit body mass, for lethality.

The D/M for lethality was about 11 cal/g (46.1 J/g). Then, on gestation day of highest sensitivity to ionizing radiation (determined previously), the authors exposed pregnant mice to the RFR at 123 mW/cm^2 (110 W/kg) for 2 to 5 minutes, corresponding to sublethal D/M values up to about 8 cal/g (33.5 J/g).

The authors remarked that they could not find any teratogenesis threshold. However, a reanalysis of their data on the percentages of resorptions and of dead, stunted, and malformed fetuses versus D/M showed the existence of a threshold: At doses less than about 3 cal/g or power densities less than about 1 mW/cm^2, 100% of the fetuses examined were normal. Above the threshold, significant percentages of abnormal fetuses were obtained, but the dependence on RFR dose was obscure.

Chernovetz et al. (1975) found that absorption of about 5 cal/g of 2.45-GHz RFR is not teratogenic to mice, a threshold considerably higher than the 3-cal/g value above. In addition, they found a lethality D/M of about 5.7 cal/g (about half the Rugh et al. value), indicating that RFR teratogenesis would occur in pregnant mice only at levels that are close to lethality for the dams.

Stavinoha et al. (1975) exposed groups of 4-day-old mice in plastic containers for 20 minutes to 10.5-MHz, 19.27-MHz, or 26.6-MHz RFR pulses (pulse duration and duty cycle not indicated) in a rectangular-coaxial transmission-line (TEM) system at an electric field strength of 5.8 kV/m. Control groups were maintained in similar containers outside the exposure chamber. The mice were weighed daily for the next 21 days. Graphs of weight versus age for each RFR frequency showed virtually no differences between exposed and control mice at corresponding ages.

In another experiment, mouse pup litters were divided into 3 groups:

(1) Control pups, kept in individual cages.

(2) Thermal-control pups, held at 37 ^{o}C for 40 minutes per day on five consecutive days.

(3) Irradiated pups, exposed to 19-MHz CW RFR for 40 minutes per day on five consecutive days in a near-field synthesizer.

The electric field was 8 kV/m, the magnetic field was 55 A/m, and the two fields were parallel (vertical) in coincident planes. Following thermal or RFR treatment, the mean increase in rectal temperature was 1.5 ^{o}C. The pups were weighed daily before each treatment and until they were 21 days old, at which time the males and females were separated. The mice were then weighed weekly for 13 additional weeks.

Statistical analyses of the growth curves showed no significant differences among the three groups of either sex. As the authors noted, although the fields were very intense, relatively little RFR energy was absorbed by the mice because their dimensions were much smaller than the wavelengths used. Thus, it would be inappropriate to apply such negative findings to humans exposed to RFR at frequencies in the same range.

Berman and coworkers (Berman et al., 1978, 1982) found a consistent effect in mice: a significantly lower mean body weight of live fetuses from dams exposed to 2.45-GHz RFR at 28.0 mW/cm^2 (22.2 W/kg) than from sham-exposed dams. However, besides the negative results of Stavinoha et al. (1975) above, other researchers could not confirm such findings or found that growth retardation was thermally induced.

With rats, Berman et al. (1981) and Smialowicz et al. (1979) found no significant differences between RFR-exposed and control groups in any of the parameters commonly looked for in such studies, even at power densities capable of heating pregnant females to temperatures over 40 ^{o}C (104 ^{o}F). This negative finding with rats led Berman et al. (1981) to conclude that mice may be more suitable than rats for seeking possible RFR-teratogenic effects in humans, a conclusion that seems specious in view of the large physiological differences between rodents and humans and among the rodent species themselves. Clearly, studies of nonhuman primates would be much more definitive.

Lary et al. (1983) treated five groups of rats on gestation day 9 as follows: The rats were euthanized on gestation day 20, at which time about two-thirds of them were found to be pregnant.

Group I was sham-exposed for 2.5 hours.

Group II was exposed to 27.12-MHz fields at 55 A/m and 300 V/m (SAR about 11 W/kg), which produced relatively rapid colonic temperature rises; exposure was terminated when the temperature reached 41.0 ^{o}C (14-22 minutes duration).

For Group III, 41.0 ^{o}C was held for an additional 2 hours by on-off switching of the RFR (total exposure time 137-144 minutes).

Exposure of Group IV was stopped when colonic temperature reached 42.0 ^{o}C (13-33 minutes).

In Group V, 42.0 ^{o}C was maintained for an additional 15 minutes by on-off RFR switching (34-55 minutes total exposure time).

Comparing the groups in succession, there were steady increases in severity in both the percentage of malformed fetuses and ratio of litters affected, with by far the largest change for the prolongation of colonic temperature at 42.0 ^{o}C. Similar results were obtained for percentages of live fetuses with visceral malformations, the largest change occurring again for prolonged exposure at 42.0 ^{o}C. The authors ascribed those teratogenic effects to the hyperthermia induced by the RFR.

Tofani et al. (1986) divided pregnant rats into four groups. The rats in group A (20 rats) were sham-exposed; those in group B (20 rats) were continuously exposed to 27.12-MHz RFR at field strengths of 20 V/m and 0.05 A/m (0.1 mW/cm^2 equivalent power density) during gestation days 0-20; and those in groups C and D (10 rats each) were similarly exposed respectively during gestation days 0-6 and 6-15. For exposure, 10 rats were co-housed in a plastic box of dimensions 80x60x35 cm, and two such boxes were used for

concurrent exposure of group B, and similarly for groups C and D. The authors estimated the SAR to be about 0.00011 W/kg. They also noted that the basal metabolic rate (BMR) for such rats is 6.51 W/kg, so the SAR was insignificant relative to the BMR.

No dead fetuses were found. Total resorptions were found in half the dams of groups B and C and in 20% of the dams in group D, with none in sham-exposed group A. The values were statistically significant for groups B and C, and nonsignificant for group D, suggesting that this effect occurs during the early stage of egg development. Mean litter weights of the three RFR-exposed groups were significantly lower than for the sham group. The only significant teratologic finding was incomplete ossification of cranial bones in the three exposure groups.

In view of the low RFR level, the authors characterized the effects as nonthermal and due to long-term exposure. However, Lu and Michaelson (1987) took issue with the exposure methodology used. They remarked the lack of description of the apparatus for providing food and water and for removing waste during exposure. They also noted that: the exposures were in the near field, the use of RFR-absorbent materials was not discussed, and the proximity of the rats to one another in the exposure boxes could have produced interactions that introduced large dosimetry uncertainties.

Lary et al. (1986) studied the dose-response relationship between RFR-induced maternal increases in body temperature and the incidence of birth defects in rats. The authors exposed groups of pregnant rats on gestation day 9 to 27.12-MHz RFR at field strengths of 55 A/m (magnetic) and 300 V/m (electric). The whole-body SAR was 10.8 W/kg. The exposures were terminated when colonic temperatures reached 41.0, 41.5, 42.0, 42.5, or 43.0 ^{o}C (10-40 minutes). Exposed and control dams were euthanized on gestation 20 and the uterine horns of each dam were examined for number of inplantations, live fetuses, and dead and absorbed conceptuses.

The numbers of various fetal abnormalities and of fetal mortality versus maternal colonic temperature on exposure termination were plotted (dose-response curves). The results indicated the existence of a colonic temperature threshold of 41.5 ^{o}C for birth defects and prenatal death.

Kaplan et al. (1982), in a primate investigation designed primarily to determine whether chronic exposure of pregnant squirrel monkeys to 2.45-GHz RFR would alter usual mother-infant behavior patterns, found no differences between RFR-exposed and sham-exposed mothers in the number of live births or the growth rates of the offspring. Unexpectedly, however, a barely significant excess of infant deaths was found in the small group (5 animals) exposed at the highest level (equivalent power density 10 mW/cm^2). To investigate this unanticipated finding, a larger study was done with possible infant death as the primary endpoint. The exposure regimen used was similar, but with a sufficient number of dams to permit adequate statistical treatment of the data. The results of this study did not confirm the previous finding of RFR-induced offspring mortality.

In summary, Rugh et al. (1974, 1975), from the results of their study involving exposure of pregnant mice to 2.45-GHz RFR at 123 mW/cm^2 (SAR about

110 W/kg) for 2 to 5 minutes on the gestation day of highest sensitivity to ionizing radiation, remarked that they could not find any teratogenesis threshold. Reanalysis of their data, however, showed the existence of a threshold: At mean total doses less than about 3 cal/g or power densities less than about 1 mW/cm^2, 100% of the fetuses examined were normal. Significant numbers of abnormal fetuses were obtained at RFR levels above that threshold, but the dependence on dose was obscure.

Chernovetz et al. (1975) found that absorption of about 5 cal/g of 2.45-GHz RFR is not teratogenic to mice, a threshold considerably higher than the 3-cal/g value above. In addition, they found that the mean total dose lethality of the dams was about 5.7 cal/g, indicating that teratogenesis would occur in pregnant mice only at levels that are close to lethality for the dams.

The study by Stavinoha et al. (1975) involving exposure of mice for 20 minutes to 10.5-MHz, 19.27-MHz, or 26.6-MHz RFR pulses at an electric field strength of 5.8 kV/m showed essentially no differences between mice exposed at each frequency and control mice in daily post-exposure weights at corresponding ages up to 21 days. Berman et al. (1978,1982) did find consistently smaller mean body weights of live mouse fetuses from dams exposed to 2.45-GHz RFR at 28.0 mW/cm^2 (22.2 W/kg), but other researchers could not confirm such findings or found that growth retardation was thermally induced. On the other hand, it is difficult to reconcile the growth retardation results of Berman et al. (1978,1982) with mice and the negative findings with rats by Berman et al. (1981) and Smialowicz et al. (1979) at RFR levels capable of heating pregnant females to temperatures over 40 ^{o}C (104 ^{o}F). Clearly, studies of nonhuman primates would be much more definitive.

Lary et al. (1983) did observe teratogenic effects in rats exposed to 27.12-MHz fields at 55 A/m and 300 V/m (SAR about 11 W/kg), but of severity that increased with colonic temperature. The largest changes were seen for prolonged exposure to maintain colonic temperature at 42.0 ^{o}C. The authors ascribed those effects to the hyperthermia induced by the RFR. The subsequent study by Lary et al. (1986) with the same RFR indicated the existence of a colonic temperature threshold of 41.5 ^{o}C for birth defects and prenatal death.

Tofani et al. (1986) reported teratogenic effects in rats exposed to 27.12-MHz RFR at field strengths of 20 V/m and 0.05 A/m (equivalent power density 0.1 mW/cm^2; author-estimated SAR about 0.00011 W/kg). They had characterized the effects as nonthermal and due to long-term exposure, but Lu and Michaelson (1987) took issue with the exposure apparatus and methodology used and with the findings.

In the Kaplan et al. (1982) study with squirrel monkeys, the excess of unexpectd infant deaths could not be confirmed in a subsequent study involving enough animals for an adequate statistical treatment of the results.

3.3.3 CONCLUSIONS

Taken collectively, the studies above indicated that teratogenic effects can occur in both nonmammalian and mammalian subjects from RFR exposure, but only at levels that produce significant temperature rises. The

results for mammals show that increases in maternal body temperature that exceed specific thresholds (41.5 ^{o}C in rats) are necessary for causing teratogenic effects.

3.4 NERVOUS SYSTEM

Concern has been expressed that direct (nonthermal) interactions of RFR with the central nervous system could produce deleterious physiologic effects. It has been postulated that such effects may be manifested as alterations in behavior, passage of foreign agents from the blood vessels in the brain into the surrounding tissue by opening of the blood-brain barrier, changes in the histopathology and histochemistry of the nervous system and of the electroencephalogram (EEG), and changes in the efflux of calcium from brain tissue.

3.4.1 BLOOD-BRAIN-BARRIER EFFECTS

In most organs and tissues of the body, molecules in the blood can freely diffuse into the tissues around capillaries. However, to protect the brain from invasion by various blood-borne microorganisms and toxic substances, there is a barrier in most regions of the brain that allows little or no movement of large fat-insoluble molecules from the blood into the surrounding brain tissues. The process is referred to as the "blood-brain barrier" (BBB). The BBB can be "opened" by certain agents (such as ionizing radiation or excessive heat) or by chemical substances (such as dimethyl sulfoxide). Studies have been done to determine if RFR can alter the permeability of the BBB in animals to substances of large molecular weight.

In an early study, Frey et al. (1975) exposed rats to 1.2-GHz pulsed RFR at 0.2 mW/cm^2 average power density (estimated SAR 0.04 W/kg) or to 1.2-GHz CW RFR at 2.4 mW/cm^2 (about 0.5 W/kg). After exposure, the rats were injected with a tracer that fluoresces in ultraviolet light, and sections of various brain regions were scored for fluorescence. The authors reported higher fluorescence scores for the rats exposed to the pulsed RFR than the CW RFR, but noted that some brain sections of sham-exposed rats also fluoresced.

In another early study, Oscar and Hawkins (1977) exposed rats to 1.3-GHz pulsed or CW RFR at levels up to 3 mW/cm^2 (about 0.6 W/kg), and measured the BBB-permeability changes to three substances that had been labeled with the radioactive tracer ^{14}C. For both RFR forms, significant levels of two of the substances were found in various brain regions, but not of the third substance.

Subsequent endeavors by Merritt et al. (1978) and by Ward and Ali (1985) to reproduce the findings of the early studies were unsuccessful. These authors concluded that the earlier results were most likely due to either artifacts introduced by the experimental techniques or flaws in the basic methodology used. Also, Preston et al. (1979) showed that RFR-induced changes in the relative sizes of the vascular and extravascular volumes in the brain could be misinterpreted as BBB alterations.

Rapoport et al. (1979) developed a method for measuring permeability of the BBB to ^{14}C-labeled sucrose about 100 times more sensitive than the

technique used by Oscar and Hawkins (1977), a method that yielded results independent of cerebral blood flow rate. With this method, Preston and Préfontaine (1980) were able to show that exposure of rats to 2.45-GHz RFR at 1 or 10 mW/cm^2 with their heads toward the source (0.1 or 1 W/kg head SAR) did not alter the permeability of the BBB to sucrose. Gruenau et al. (1982) confirmed the negative findings of Preston and Préfontaine (1980), but for rat exposures to 2.8-GHz pulsed RFR (2-μs pulses, 500 pps) at average power densities up to 15 mW/cm^2 (3 W/kg) and CW RFR up to 40 mW/cm^2 (8 W/kg).

In other studies, such as by Ward et al. (1982), in which results with RFR were compared with those for substances known to open the BBB as positive controls (such as urea), the findings were negative unless the brain had been rendered hyperthermic.

In four comprehensive studies, Williams et al. (1984a,b,c,d) exposed groups of conscious, unrestrained rats to 2.45-GHz RFR and used a variety of tracers and methods for detecting penetration of the BBB. They also determined the relationship of BBB changes to colonic temperature and the temperatures in several brain regions after exposure at levels up to 65 mW/cm^2 (13 W/kg) or to ambient heating at 42 ^oC. At 20 mW/cm^2 (4 W/kg) and lower, no penetration was seen in those brain regions where the BBB is normally effective. The authors concluded that at the latter level, the thermoregulatory mechanisms of the rat are more than adequate for maintaining body temperatures well within tolerable limits, including brain temperatures, but that exposure to intense fields for long periods could approach or exceed such limits.

Neilly and Lin (1986) investigated the possible synergism between ethanol (which does not alter the BBB at normal intoxication levels) and levels of RFR sufficient to disrupt the BBB, using Evans blue dye as the tracer. Groups of rats were anesthetized with pentobarbital. Each rat was placed on a heating pad to hold its colonic temperature near 37.5 ^oC, and a catheter was inserted into its left femoral vein. When the colonic temperature of the rat reached between 37.2 ^oC and 37.5 ^oC, the rat was perfused through the catheter with a specified dose of prewarmed ethanol. Each group of rats was given a different ethanol dose within a specific range. When the colonic temperature stabilized at 37.0 ^oC (usually 1-3 minutes after perfusion), the left side of the rat's head was exposed to 3.15-GHz CW RFR with an applicator at a net (forward minus reflected) power of 3,000 mW/cm^2 for 15 minutes. A control group was perfused with saline instead of ethanol.

Following treatment, each rat was perfused with prewarmed Evans blue dye. After enough time had elapsed for dye circulation, the excess dye was washed out with saline, and the brain was removed. Each brain was scored for surface staining by the dye. The brain was then sliced into thin sections and each section was scored for internal staining.

In separate experiments, rats were similarly prepared but during the 15 minutes of RFR exposure and for 5 minutes afterward, brain temperature was measured with a non-perturbing probe inserted through a small hole burred in the cranium before exposure. Rectal temperatures were also recorded.

The brain temperature of each rat rose to a plateau within the first few minutes of exposure, and remained there for the rest of the exposure. It then fell to pre-exposure level during the 5 minutes after exposure. The mean plateau temperature was highest (about 49 ^{o}C) for the group given the lowest ethanol dose and it decreased steadily with increased ethanol dose to the lowest value (about 43 ^{o}C) for the rats given the highest ethanol dose. The mean colonic temperatures of the various rat groups did not differ significantly from one another.

The results indicated that disruption of the BBB by the RFR was due to elevation of brain temperature. The authors concluded that, depending on dosage, ethanol can inhibit such disruption of the BBB by moderating the increases in brain temperature produced by the RFR. They ascribed the action of ethanol to physiologic cooling of the RFR-exposed region of the brain, and cited references indicating that ethanol and pentobarbital can act synergistically.

3.4.1.1 SUMMARY

In summary, the early studies by Frey et al. (1975) and Oscar and Hawkins (1977) can be disregarded because of evidence of artifact in the methods used in the experiments. Moreover, Merritt et al. (1978) and Ward and Ali (1985) were unable to reproduce those findings, and Preston et al. (1979) showed that certain specific RFR-induced changes in the brain could be interpreted wrongly as BBB alterations. Using the method of Rapoport et al. (1979), Preston and Préfontaine (1980) and Gruenau et al. (1982) obtained negative findings regarding RFR-induced alterations of the BBB. The four comprehensive studies by Williams et al. (1984a,b,c,d) with conscious unrestrained rats, in which several different tracers and methods were used for detecting BBB penetration, also yielded negative findings. Neilly and Lin (1986) showed that disruption of the rat BBB at high RFR levels is due to elevation of brain temperature. In addition, they found that high ethanol doses inhibits BBB disruption by moderating the increases in brain temperature produced by the RFR.

3.4.2 HISTOPATHOLOGY AND HISTOCHEMISTRY OF THE CENTRAL NERVOUS SYSTEM

Neural histopathologic and histochemical studies are, respectively, those of diseased or damaged neural tissues, and the chemical composition of such tissues. RFR effects have been sought *in vitro*, on preparations of neural tissues excised and kept alive in appropriate solutions while undergoing RFR exposure, and *in vivo*, from exposure of live animals.

3.4.2.1 HISTOLOGICAL AND HISTOCHEMICAL STUDIES IN VITRO

In several histological studies, preparations of neural tissue were exposed to RFR in vitro. Courtney et al. (1975) excised superior cervical ganglia from white rabbits, stretched them singly across a vertical section of waveguide sealed at the bottom with a quarter-wave dielectric plate and filled with Ringer's solution, and exposed each ganglion to 2.45-GHz CW RFR from below. The calculated normalized SAR of the ganglion was 2.2 W/kg per mW/cm^2. The preganglionic end was connected to a set of stimulating electrodes outside

the waveguide, and contact with the postganglionic end was made via a glass capillary through a wall of the waveguide. Ringer's solution at 37 ^{o}C was pumped through the waveguide section.

Each ganglion was exposed to RFR at power densities up to about 300 mW/cm^2 (660 W/kg) for 1-minute intervals, with 1 minute between exposures for control measurements. The authors noted that only above about 100 W/kg did the temperature rise of the Ringer's solution exiting the waveguide exceed 0.1 ^{o}C. During the exposure and control intervals, the ganglion was stimulated with 100-300 μs pulses at 1 pps, and the response latencies for synaptic transmission of the B fiber (short latency) and the C fiber (long latency) were determined. There were no significant changes in the mean response latencies from the RFR at SARs up to 660 W/kg.

Chou and Guy (1978) similarly studied the rabbit vagus nerve and the cat-saphenous nerve, as well as the rabbitt superior cervical ganglion. As in Courtney et al. (1975), each ganglion or vagus nerve was mounted within a vertical waveguide section (parallel or perpendicular to the E-vector) through which Ringer's solution was pumped. The solution temperature at the fluid outlet of the waveguide was held constant at 37 +/- 0.02 ^{o}C during exposure to the RFR. At the high RFR levels, however, the fluid temperature at the center of the specimen (measured with a nonperturbing probe) rose by up to 1 ^{o}C because of the limited circulation rate of the fluid pump.

Each specimen was stimulated with a 0.3-millisecond current pulse of 0.3-30 mA at 2-second intervals before, during, and after exposure to RFR. The compound action potentials (CAPs) were recorded and their conduction velocity and amplitude were determined. Vagus nerves were exposed to 1-μs pulses of 2.45-GHz RFR at 1000 pps or 10-μs pulses at 100 pps for 10-minute periods at average SARs of 0.3, 3, 30, and 220 W/kg or to CW RFR at the same SARs, with 5 minutes between exposures. Superior cervical ganglia were exposed for only 5-minute periods because of their shorter lifetimes. Specimens were also exposed to pulsed RFR at 220 W/kg average (220 kW/kg peak) and to CW RFR at 1500 W/kg with no current-pulse stimulation, to test for the possibility of direct RFR stimulation.

No direct stimulatory effects of RFR exposure were observed at the highest available SARs (pulsed RFR at 220 kW/kg peak or CW RFR at 1500 W/kg) in the absence of stimulation by current pulses. With electrical stimulation, no changes in amplitude or conduction velocity of the CAPs were seen for exposures of rabbit superior cervical ganglia or vagus nerves to pulsed or CW RFR at SARs that did not increase the fluid temperature near the center of the specimen.

The conduction velocity and peak CAP amplitude versus time was shown for a representative cat saphenous nerve exposed to the CW RFR at 1500 W/kg, an SAR that increased the fluid temperature by 1 ^{o}C. The conduction velocity rose by about 2% during exposure, a result reproduced by raising the temperature of the solution 1 ^{o}C by non-RFR means. The variations in peak CAP amplitude were small and apparently not RFR-dependent. Similar data were shown for a representative stimulated rabbit vagus nerve before, during, and after exposure to 10-μs pulses (100 pps) at 220 kW/kg peak, and to CW RFR at 1500 W/kg. For the pulsed RFR, the fluid temperature rose 0.3 ^{o}C, which

increased the conduction velocity slightly (from 117 to 118 m/s). For the CW RFR, the fluid temperature rose by 1 ^{o}C, which increased the conduction velocity from 117 to 135 m/s. An equivalent rise in fluid temperature by non-RFR means yielded the same velocity increase.

CAP recordings for a rabbit superior cervical ganglion exposed to 1-μs pulses (1000 pps) and to CW RFR at the same SARs as the vagus nerve were also shown. For the pulsed RFR, the fluid-temperature rise was again 0.3 ^{o}C, but the latency time remained unchanged. The rise in fluid temperature by the CW RFR was again 1 ^{o}C, and the latency time decreased to 16 ms, a result reproduced by raising the fluid temperature 1 ^{o}C by non-RFR means.

Among the histochemical effects sought *in vitro* were RFR-induced alterations in the activities of the enzymes acetylcholinesterase (AChE) and creatine phosphokinase (CPK) in rabbit blood. Olcerst and Rabinowitz (1978) found that 2.45-GHz RFR significantly decreased AChE activity, but only at a level sufficient to denature AChE (about 125 mW/cm^2). Galvin et al. (1981c) observed that 2.45-GHz RFR did not affect the activity of either AChE or CPK at SARs up to 100 W/kg.

3.4.2.2 HISTOLOGICAL AND HISTOCHEMICAL STUDIES IN VIVO

Albert et al. (1981) indicated that prenatal development of the mammalian brain depends on migration of nerve cells, and specifically that a readily identifiable cell class in the cerebellum called Purkinje cells arise during the second half of gestation. They sought possible effects of prenatal and postnatal exposure to RFR of rats on such cells.

In one experiment, two groups of 3 pregnant rats each were exposed to 2.45-GHz RFR at 10 mW/cm^2 for 5 days starting on gestation day 17. The mean SAR was estimated as about 2 W/kg, with a range 0.8 to 6 W/kg due to rat movements. Six other rats were sham-exposed. Three of the 6 pups of each group were euthanized on postnatal day 1 and the other 3 of each group were euthanized 40 days after birth. The cerebella from the day-1 pups were not mature enough for clear discernment of the Purkinje cells, but the mean Purkinje cell counts for the RFR-exposed 40-day pups were much lower than for the sham-exposed 40-day pups. The latter result was taken as indicating the permanence of this prenatal-exposure effect.

In another experiment, 1 pup each of 6 pairs of litter mates was exposed to the RFR for 5 days, 7 hours per day, while the other pup was sham-exposed. Three pups of each group were euthanized immediately and the other three of each group were euthanized 40 days later. In the groups euthanized immediately, the mean Purkinje-cell count for the rat pups exposed to the RFR was significantly lower than for those sham-exposed, but the mean counts for the 40-day RFR-exposed and sham-exposed pups did not differ significantly. The authors regarded those results as indicating the reversibility of the effect.

The statistical validity of the positive results above is open to question because of the large SAR variations noted by the authors. They also did a similar study on squirrel monkeys that previously had been exposed perinatally elsewhere, which yielded no significant differences between RFR-

and sham-exposed groups in whole-body mass, brain mass or volume, or in counts of Purkinje cells.

Merritt and Frazer (1975) exposed mice for 10 minutes to 19-MHz RFR consisting of either an electric field at 6 kV/m with associated magnetic field of 6.4 A/m, or a magnetic field at 41 A/m with 2 kV/m associated electric field, exposures that did not increase rectal temperature. The objective was to determine whether such fields can alter the levels of specific neurotransmitters in the mouse brain.

Fifteen minutes after the 19-MHz exposure, the head of each mouse was exposed to intense microwave RFR to quickly inactivate its brain enzymes, a method that produced a rise in brain temperature of 40 to 50 ^{o}C in 1 second. Sham-exposed mice were similarly treated. After such inactivation, the brains were assayed for the levels of serotonin (5HT) and its metabolite 5-hydroxyindole acetic acid (5HIAA), dopamine (DA) and its metabolite homovanillic acid (HVA), and norepinephrine (NE). There were no significant differences between the sham-exposed controls and those exposed to either the E-field or H-field in the mean whole-brain concentrations for any of the neurotransmitters or their metabolites.

Sanders et al. (1980) investigated the hypothesis whether exposure of brain tissue to RFR *in vivo* results in inhibition of the respiratory chain function followed by decreases in concentrations of adenosine triphosphate (ATP) and creatine phosphate (CP). The authors noted that the reduction of nicotinamide adenine dinucleotide (NAD) to NADH by proton addition can be monitored *in situ* continuously by fluorescence measurements, i.e., by excitation at 366 nm and observation of NADH fluorescence at 460 nm, using a time-sharing fluorimeter. Thus, if RFR exposure stresses the cells that inhibit respiratory chain function or cell functions that utilize ATP and CP, the NADH level will increase.

Rats were anesthetized with sodium pentobarbital, the scalp and muscles at the side of the skull were removed, and a 4x8-mm aperture was made through the skull, leaving the dura intact. The head of the rat was held rigidly in place, the light from a 366-nm excitation source was focused to a spot (1-2 mm) on the cerebral cortex, and a fiber-optic bundle was directed toward the focal spot. The other end of the fiber-optic bundle was terminated at a wheel that housed a 460-nm filter for NADH-fluorescence measurements and a 366-nm filter for measuring reflectance of the incident beam from the surface.

After preparation, the rat was exposed to 591-MHz CW RFR in the far field of a horn, with the electric vector parallel to the long axis of the rat. The radiation pattern of the horn was such that only the head of the rat was exposed. The incident power densities at the exposure site were measured with a radiation detection meter, and theoretical models were used to estimate SARs. Maximum SARs at the surface of a 2.0-cm diameter sphere and a semi-infinite plane of brain tissue respectively were 0.026 and 0.16 W/kg per mW/cm^2.

In a baseline experiment, NADH fluorescence and reflectance levels were determined in several rats before exposure. When the baseline NADH

fluorescence level was steady for 5 minutes, exposure to 591-MHz RFR for 5 minutes at 13.8 mW/cm^2 was begun. The reflectance trace for the excitation beam showed no significant deviation from baseline level during the entire RFR exposure period. The fluorescence results for one rat were displayed graphically: The intensity of the trace began to rise on RFR initiation; it reached a maximum of 12.5% above baseline level at 30 seconds, showed a compensatory partial return toward baseline during the next 2.5 minutes, followed by a slow rise during the remaining 2 minutes. The authors noted that the 30-second maxima for the rats tested were in the range 4% to 12.5% above baseline.

Groups of rats given the same pre-exposure treatment as in the baseline experiment were sham-exposed or exposed at 13.8 mW/cm^2 for 0.5, 1, 2, 3, or 5 minutes, during which NADH fluorescence was measured. Right after RFR- or sham-exposure, the head and neck of each rat were immersed in liquid nitrogen for at least 2 minutes, and the frozen head was removed and stored in liquid nitrogen. Later, the frozen cerebral hemisphere near the aperture in the skull was extracted and pulverized, and duplicate aliquots were assayed for ATP and CP. Other groups of rats were sham-exposed or exposed at 5.0 mW/cm^2 for 0.5 or 1 minute and similarly processed. Not indicated was why the contralateral cerebral hemispheres were not also assayed for comparison.

Mean ATP and CP concentrations as percentages of baseline levels and their standard errors were graphed versus duration of sham-exposure or RFR exposure at 13.8 mW/cm^2. The sham-exposures yielded no statistically significant percentage changes in either mean ATP or mean CP level relative to baseline. With the RFR, however, 30-second exposures yielded the lowest mean ATP level, about 75% of baseline. For the longer exposures, the mean ATP levels were higher but did not exceed about 90% of baseline. The 30-second RFR exposures also yielded the lowest mean CP level, about 60% of baseline. The 3-minute exposures yielded a relative maximum of 85% of baseline and the 5-minute exposures showed a decrease to 60% again. By Student t-test, all of those percentage differences in mean ATP and CP between the RFR and sham groups at corresponding times were significant, most at the $p<0.005$ level.

The results for exposure at 0 (sham), 5, and 13.8 mW/cm^2 for durations of 0.5 and 1 minute were tabulated in terms of mean ATP and CP levels (in micromoles/g), standard errors, and numbers of rats. By t-test, the mean ATP and CP levels at 5 mW/cm^2 and 13.8 $mW/cm2$ for either duration differed significantly from their corresponding sham-exposure levels. However, the differences in mean ATP level between exposure at 5 mW/cm^2 and 13.8 mW/cm^2 for corresponding durations were both nonsignificant. This was also true for the CP results. Both of the latter findings appear to indicate that the effect is not dose-dependent, or that it saturates below 5 mW/cm^2.

Temperatures at depths 2-3 mm below the brain's surface were measured with a thermistor placed on top of the brain just under the dura, adjacent to the focal spot of the excitation light, with the leads at right angles to the electric vector. Rats other than those used in the NADH, ATP, and CP assays were exposed at 0, 13.8, 18.0, 30.0, 40.0, and 47.0 mW/cm^2 for 5 minutes. With sham-exposure, heat loss through the aperture in the skull was found to cause a decrease in brain temperature of 0.7 ^oC at the end of the period. For exposure at 13.8 mW/cm^2, a decrease of 0.6 ^oC was observed at exposure end, a

value close to that for sham-exposure, presumably an indication that the RFR at that level had added little heat. Decreases of 0.5 and 0.1 ^{o}C were observed at 18.0 and 30.0 mW/cm^2, respectively, and increases of 0.2 and 0.1 ^{o}C were obtained at 40.0 and 47.0 mW/cm^2. Rectal temperatures remained constant at all exposure levels.

From those results, the authors concluded that the observed changes in mean ATP and CP levels at 5 or 13.8 mW/cm^2 could not be ascribed to general tissue hyperthermia (but local hyperthermia was not excluded). Instead, the data support the hypothesis that RFR inhibits electron transport chain function in brain mitochondria, thereby decreasing brain energy levels.

Subsequently, Sanders and Joines (1984) investigated the effects of hyperthermia alone and in conjunction with RFR. Rats were anesthetized with urethane instead of sodium pentobarbital (used in the previous study) "to avoid barbiturate effects on brain energy metabolism". Rat preparation was similar to that previously used, except that the fiber-optic bundle was bifurcated near the measurement end; one arm served to convey 460-nm light from the brain to the apparatus for measuring NADH fluorescence and the other arm conveyed 549-nm light to the apparatus for measuring general brain fluorescence.

Groups of anesthetized rats were exposed to 591-MHz CW RFR for up to 5 minutes at 13.8 mW/cm^2. Upper and lower limits of spatial-average SAR in the brain were estimated in this paper to be 0.42 and 0.18 W/kg per mW/cm^2, or 5.8 and 2.5 W/kg at 13.8 mW/cm^2. Also, temperatures were measured with a thermistor at a point about 2 mm below the surface of the brain during exposure at 60 and 100 mW/cm^2, and the rates of temperature increase were used to estimate the local normalized SAR. The results for the two power densities were 0.613 and 0.626 W/kg per mW/cm^2, yielding a local SAR of about 8.5 W/kg for 13.8 mW/cm^2, or more than threefold higher than the spatial average SAR.

Other groups were subjected only to brain hyperthermia, and still others to combined hyperthermia and RFR. In both sets of hyperthermia experiments, brain temperatures were held constant by use of heater pads and a temperature regulator. However, the method used to maintain brain temperatures constant was not described; the authors only stated: "The temperature regulator was adjusted so that power would turn off when the selected temperature (35.6 or 37 or 39 ^{o}C) was reached."

In an auxiliary experiment, ATP and CP assays of RFR-exposed rats anesthetized with urethane were compared with similar assays of RFR-exposed rats anesthetized with sodium pentobarbital, with the brains of both groups held at 35.6 ^{o}C. The maximum deviation was 4.5%.

In the hyperthermia-only experiments, brain temperatures of urethane-anesthetized, sham-exposed rats were held at 35.6 ^{o}C. ATP and CP assays yielded mean concentrations that did not differ significantly from those reported in Sanders et al. (1980). Groups were then sham-exposed with brain temperatures held at 37.0, 39.0, or 41.0 ^{o}C, and the mean ATP and CP concentrations versus brain temperature were plotted as percentages of the concentrations at 35.6 ^{o}C. The percentages of both ATP and CP declined steadily with increases in brain temperature, with the CP rate of decline

higher. At 39 °C, ATP and CP decreased to about 90% and 70%, respectively; at 41 °C, the decreases were to about 70% and 45%, respectively.

Rats with brain temperatures held at 35.6 °C were exposed at 13.8 mW/cm^2 for 0.5 to 5 minutes, and the percentage increase in NADH and mean percentages of ATP and CP (relative to the concentrations at 35.6 °C for sham-exposed rats) were plotted versus exposure duration. The results for 30-second exposures showed the largest decreases, to about 75% for ATP and to about 60% for CP. A similar set of experiments was done with brain temperatures held at 39.0 °C (RFR plus hyperthermia). At 0 minutes, the ATP and CP levels were respectively about 90% and 70%, decreases ascribed to the hyperthermia, and the levels declined further to minima of about 60% and 45% for 1-minute exposures. For 5-minute exposures, the ATP level rose to about 80% and the CP level rose to about 50%.

The general conclusion was: "The decreases in ATP and CP in the 39 °C brain during microwave exposure were significant and resulted in ATP and CP being much lower than observed at 35.6 °C. Thus, at 39 °C when the brain metabolic rate was increased, subsequent microwave exposure rapidly induced further decreases in ATP and CP, similar to the 35.6 °C microwave exposure data, ie, without a further increase in brain temperature; [these results] are consistent with the concept of direct microwave inhibition of energy metabolism." The latter statement seems open to question, however, because with an estimated local SAR of 8.5 W/kg at 13.8 mW/cm^2, considerable local heating must have occurred.

Sanders et al. (1984) performed similar experiments, but at 200 MHz and 2,450 MHz as well as 591 MHz. Rats (surgically prepared as in the previous studies) were exposed to RFR in a microstrip transmission line system having a 6-cm plate separation, with the anesthetized rat placed on the ground plane. Power densities at the position of the rat's head (with the rat absent) were measured with a Raham radiation hazard meter.

Local SARs at a depth of 2-3 mm below the top surface of the brain of a dead rat were determined from measurements of temperature rise versus time with a Vitek isotropic probe during exposure of the carcass to each frequency at 60 and 100 mW/cm^2. The normalized SARs at 200, 591, and 2,450 MHz were 0.046, 0.185, and 0.368 W/kg per mW/cm^2.

The brain temperature at the same depth was measured with the Vitek probe in urethane-anesthetized rats. The authors noted that ATP and CP concentrations did not change significantly when brain temperature varied by 0.4 °C and that urethane lowers the rat's body temperature to about 35.5 °C. For this reason, they maintained brain temperature at 35.6 ± 0.3 °C with a hot air blower directed into the microstrip toward the rat.

For the NADH fluorescence part of the study, a group of 6 rats was exposed at each RFR frequency. Each rat was given 2-minute exposures at increasing power densities in the range 0.5 to 20.0 mW/cm^2 (with 2 rats also given 40.0 mW/cm^2), and its NADH fluorescence was measured after each exposure. NADH fluorescence returned to baseline between exposures. Since NADH fluorescence had been found to peak for 30-second exposures and was much

lower for 2-minute exposures, it is not clear why 2-minute exposures were used in these experiments.

The differences in NADH results among the 6 rats of each group were large, so their data were not combined for statistical treatment. Instead, the percentage changes in NADH versus power density were tabulated for each rat, with each serving as its own control. The 200-MHz data for each rat showed steady increases in NADH with power density, indicative of a dose-response relationship, with a trend toward saturation at the higher power densities. The results for 591 MHz were similar. However, no NADH changes were detected for 2,450 MHz, from which the authors suggested that the effect is frequency-dependent.

Using the dielectric constant and conductivity at each frequency, the authors converted power densities into tissue field strengths, from which they surmised that the electric field is the operative parameter. By extrapolating the graphs of NADH change versus electric field strength to zero effect, they found a threshold of 3-5 V/m for both 200 and 591 MHz.

Whole-brain mean assays of ATP and CP for exposure to 200, 591, and 2,450 MHz at 13.8 mW/cm^2 versus exposure duration were shown graphically as percentages of baseline values. The largest effects were for 30-second exposures to either 200 MHz or 591 MHz; the levels of ATP decreased to about 80% and 75% of baseline for the two frequencies, respectively, and rose for exposures of longer durations. The mean CP assays showed no significant changes for 200 MHz, but a decrease to about 60% of baseline for 30-second exposures. No significant changes in either ATP or CP were seen at 2,450 MHz.

In yet another study, Sanders et al. (1985) compared the effects of exposing the heads of anesthetized rats to unmodulated, sinusoidally-amplitude-modulated, and pulsed 591-MHz RFR for 5 minutes at 10 or 20 mW/cm^2 (1.8 or 3.6 W/kg) on NADH fluorescence. The authors indicated that the mean brain temperature of the anesthetized rat before exposure was 35.6 ^{o}C, and that at the end of 5 minutes of exposure at 13.8 mW/cm^2, the mean temperature was 0.27 ^{o}C lower. Thus, they remarked that the RFR exposures were not hyperthermic. As in Sanders et al. (1984), because of large differences in brain vascularity among the rats, each rat was used as its own reference: The change in NADH fluorescence of each rat following exposure at each level was expressed as a percentage of its preexposure (baseline) value.

In the sinusoidal-modulation experiments, the modulation frequencies were in the range 4-32 Hz in 4-Hz steps and at 100% modulation. The mean percentage increases in NADH fluorescence versus modulation frequency were plotted for the two RFR levels separately. The mean NADH fluorescence at 20 mW/cm^2 was 9% higher than the mean baseline for modulations at 4 and 8 Hz; it increased to about 10% for modulation at 12 Hz, and rose to a maximum of 11% at 24 Hz; it then decreased to slightly less than 9% at 32 Hz. The changes at 10 mW/cm^2 were similar but smaller, ranging from 4.5% above baseline at 4 Hz to a flat maximum of 5.5% at 16, 20, and 24 Hz, then a decrease to slightly less than 4.5% at 32 Hz. The SEs at both RFR levels were about 10% of the means. By analysis of variance and comparison of treatment to control, both the effect of exposure and the difference in exposure level were significant.

However, although the data on modulation frequencies seemed to indicate a trend, the difference across modulation frequency was nonsignificant.

In the pulsed-RFR experiments, the exposures were to 5-μs pulses at 500 or 250 pps at average power densities in the range 0.5-13.8 mW/cm^2 (0.09-2.5 W/kg). The percentage increase in NADH fluorescence was shown graphically versus average power density for each of four rats exposed to 500 pps. The curves were similar in shape, but at each RFR level, the rat that showed the largest responses had percentage increases about twice those for the rat with the smallest responses (about 8% versus 4% at 13.8 mW/cm^2). Thus, the results varied considerably from rat to rat even though each rat was used as its own reference. However, the curves did indicate the existence of a dose-response relationship, with a threshold for effect in the range 0.4 to 0.5 mW/cm^2 (0.07-0.09 W/kg).

Also shown was the curve for one of two rats given 250 pps. At 13.8 mW/cm^2, its increase in NADH fluorescence was about 5%, but its threshold was within the range 1.8-1.9 mW/cm^2 (0.33-0.34 W/kg), about fourfold higher than for the rats given 500 pps. By analyses of variance, the NADH data for the rats given 250 and 500 pps showed a significant effect of exposure for each type of modulation.

The effects of CW, 16-Hz amplitude-modulated, and pulsed (500 pps) 591-GHz RFR, all at 13.8 mW/cm^2 (2.5 W/kg) for 0, 0.5, 1, and 5 minutes on the mean ATP and CP concentrations were tabulated for comparison. For the corresponding durations of each exposure mode, the differences were not significant.

Lai et al. (1988) studied the results of single, 45-minute exposures of rats to 2.45-GHz CW or pulsed RFR (2-μs pulses at 500 pps) on choline uptake in several regions of the brain, the uptake being a measure of cholinergic activity. Exposures were done in groups of four individual cylindrical waveguide chambers (Guy et al., 1979) to circularly-polarized RFR, or in a miniature anechoic exposure chamber (Guy, 1979) to plane-polarized RFR. The exposure levels were set to yield a whole-body SAR of 0.6 W/kg (1.0 or 2.07 mW/cm^2, respectively). Control rats were sham-exposed in the same chambers.

From a dosimetry study by Chou et al. (1985), 0.6-W/kg whole-body SAR in a cylindrical waveguide yields a spatial mean SAR in the head of 0.77 W/kg with the rat facing the RFR source and 0.91 W/kg with the tail facing the source. On the other hand, for a rat exposed dorsally in the anechoic chamber from above (with the top of its body toward the source) and its body axis parallel to the electric vector, the spatial mean SAR in the head corresponding to 0.6-W/kg whole-body SAR is 0.56 W/kg.

All four exposure conditions yielded decreases in choline uptake in the frontal cortex, with no significant differences between the CW and pulsed RFR. Decreases in choline uptake were seen in the hippocampus for exposures to the pulsed RFR in both types of chamber but not to the CW RFR in either type of chamber. Choline uptake decreased in the striatum from exposure to pulsed or CW RFR in the anechoic chamber but not in the waveguide chambers.

On the other hand, no significant changes in choline uptake in the hypothalamus were seen for any of the exposure situations.

The authors suggested that the differences in results for the CW and pulsed RFR could be ascribed to the RFR auditory effect, noting that the characteristics of the pulsed RFR used were above the threshold for that effect. They did not suggest specific mechanisms for the other results.

3.4.2.3 SUMMARY

In summary, Albert et al. (1981) had reported lower mean counts of Purkinje cells in 40-day pups RFR-exposed for 5 days *in utero* to 2.45-GHz RFR at 10 mW/cm^2 relative to counts for sham-exposed pups, results that are open to question because of the large variations in SAR (0.8 to 6 W/kg, 2 W/kg estimated mean) due to movement of the dams during exposure. Also, rat pups exposed to the RFR and euthanized 40 days later did not show such differences, and little credence can be given to their results for rat pups euthanized right after exposure because of Purkinje cell immaturity in neonates, a point previously mentioned by the authors. Moreover, in a similar study they did on squirrel monkeys that had been previously exposed perinatally elsewhere, they found no significant differences between RFR-exposed and sham-exposed monkeys in Purkinje cell counts.

Merritt and Frazer (1975) obtained negative findings in mean brain concentrations of various neurotransmitters and their metabolites assayed in mice exposed to predominantly electric or magnetic fields at 19 MHz. However, the authors noted that at 19 MHz, a mouse absorbs very little energy from either field.

Sanders and coworkers observed increases in NADH fluorescence and reductions of ATP and CP concentrations in the rat brain by RFR at levels characterized as not producing measurable brain hyperthermia. Although some points are open to question, those positive findings appear to be valid, and are worthy of further study. The experiments were performed on anesthetized rats, with consequent lowering of brain temperatures. Whether similar results would occur in the absence of anesthesia has not been determined. It is noteworthy that the effects were higher at 591 MHz than at 200 MHz and that they were not observed at 2.45 GHz, suggestive of dependence on RFR frequency.

A study by Lai et al. (1988) with 2.45-GHz CW and pulsed RFR at whole-body SARs of about 0.6 W/kg on choline uptake in various regions of the rat brain yielded both positive and negative results. However, not clear were the apparent inconsistencies in results for the two kinds of exposure chamber and between pulsed and CW RFR.

In conclusion, although histopathological and histochemical changes in the central nervous system were seen at relatively low SARs by Sanders and coworkers and Lai et al. (1988), their significance with regard to possible human health hazards is not clear, and the questions above about those studies remain open. Overall, considering other experimental results in which the effects observed were ascribed to local increases in brain temperature, it seems unlikely that exposure to RFR levels that do not increase local brain

temperatures would cause any histopathological or histochemical changes in the human central nervous system.

3.4.3 EEG- AND EVOKED-RESPONSE CHANGES

Various studies have been conducted on the effects of exposure of animals to RFR on the electroencephalogram (EEG) and/or stimulus-evoked responses (ERs). In many early studies, metallic electrodes were either attached to the scalp or implanted in the brain prior to exposure of the animal to RFR, and were present during exposure. Johnson and Guy (1972) pointed out that such metallic electrodes can grossly perturb the fields and produce greatly enhanced energy absorption in tissues in the immediate vicinity of the electrodes, thereby yielding false or misleading results. In such local regions, the greatly enhanced fields are also likely to cause artifacts in the function of nerve tissue because of high sensitivity of such tissue to electrical stimulation by induced currents.

Artifacts in tissue should not be confused with possible recording artifacts in EEGs or ERs produced by pickup of fields by the electrodes and leads during exposure of the animal. Recording artifacts have been avoided by making the recordings before and after exposure, but at the expense of not observing effects that may occur only during exposure or effects having considerably different characteristics during exposure than before or after exposure. Usually such artifacts can be rendered negligible by appropriate filtering, but field-enhancement biological artifacts cannot. It is also noteworthy that many of the EEG and ER studies were done on heavily sedated animals, usually with barbiturates. Therefore, their responses may not necessarily reflect those expected in normal alert animals.

Essentially all of the early studies on this topic were flawed for various biological as well as engineering reasons, rendering their findings suspect. To diminish enhancement and recording artifacts, Tyazhelov et al. (1977) developed electrodes of high linear electrical resistance, and used appropriate filtering of the recorded EEG signals. Chou and Guy (1979a) studied two types of nonperturbing electrodes for recording EEGs during chronic exposure to RFR. One type consisted of a fine carbon-loaded-Teflon wire for use as a conductive lead and as a subcortical electrode; one end of the wire was passed through a glass pipette 2.5 cm long, with 0.5 mm protruding as the electrode proper, a configuration similar to one in a nonperturbing temperature probe developed by Bowman (1976). The other type, for use as a cortical electrode, consisted of a thin screw 4.5 mm long machined from carbon-loaded Teflon, with a carbon-loaded-Teflon lead squeezed tightly onto the screw by a nylon nut, using conductive glue to ensure good electrical contact. The other end of the lead from either type was attached with conductive glue to a metal pin, the latter to permit quick connection to a head plug.

For electrode implantation, Chou and Guy (1979a) anesthetized rabbits with sodium pentobarbital and drilled and threaded a small hole in the calvarium. One carbon-loaded-Teflon screw was placed near the sensory-motor cortex; another carbon-loaded-Teflon screw was placed in the area of the nasal bone as the reference electrode. The subcortical electrode was implanted so

that its tip entered the hypothalamus. All of the metal pins at the other ends of the leads were connected to a Winchester plug.

EEG measurements made, in the absence of RFR, with carbon-loaded-Teflon electrodes implanted in rabbits did not differ significantly from those with similarly implanted stainless-steel electrodes when a 60-Hz filter is used with the Teflon electrodes. Four to six months after Teflon electrode implantation, there was no observable tissue damage. The authors concluded that such electrodes would be useful for chronic EEG recording in animals exposed to RFR.

Chou et al. (1982) implanted such electrodes in the sensory-motor, occipital, and nasal regions of 18 rabbits, with the electrodes in contact with the dura. Six of the rabbits were exposed individually from above in a miniature anechoic chamber to 2.45-GHz CW RFR at 1.5 mW/cm^2 with its long axis parallel to the electric vector for 2 hours per day, 5 days/week, for 90 days. Six other rabbits were exposed to 2.45-GHz pulsed RFR (10-μs pulses at 100 pps) at the same average level in a similar chamber for the same durations. By thermography in the sagittal plane of a euthanized rabbit, two "hot spots" were seen, one in the sinus area and the other on the back. The corresponding peak SARs in those regions were respectively 2.1 and 1.6 W/kg at 1.5 mW/cm^2. The remaining 6 rabbits were sham-exposed in still another chamber of the same kind for the same durations.

Body weights were measured every other day and found to increase almost linearly during the 3-month treatment period, at which time the weights were reaching a plateau. The differences among the three groups were statistically nonsignificant. Results of hematological, chemical, and morphological tests of blood samples taken monthly were tabulated. Those showed no significant differences among the groups. The eyes were examined with a slit lamp before and after the 3-month treatment. No cataracts had developed in any of the 18 rabbits.

The EEGs and evoked responses (ERs) were recorded with the implanted electrodes every Friday after the 2-hour treatment. The authors noted that the frequency spectrum varied considerably from rabbit to rabbit and from one recording session to another for each rabbit, rendering it impossible to compare specific EEG or ER frequencies among the animals. Nevertheless, statistical tests showed no significant differences among the three groups.

Kaplan et al. (1982) conducted a study directed primarily toward seeking any effects on infant behavior of squirrel monkeys of perinatal exposure to 2.45-GHz RFR at whole-body SARs up to 3.4 W/kg (see Section 3.7.1.2), but they also recorded EEGs and visually evoked responses (VERs). No chronically attached or indwelling electrodes were used during exposure. Instead, baseline EEGs and VERs were obtained from mothers and infants of all groups at the time of weaning (when the infants were 6 months old), and at ages 9 and 12 months from infants that had been perinatally sham-exposed or exposed to the RFR.

No data were presented, but the authors indicated that statistical analyses revealed no differences among the various RFR-exposed and sham-exposed groups on any of the obtained measures.

3.4.3.1 SUMMARY

In overall summary, various studies have been done to ascertain the effects of RFR on the EEG or the responses evoked by visual or auditory stimuli (ERs). As demonstrated by Johnson and Guy (1972), the use of indwelling metallic electrodes, wires, or screws may be questioned as a procedure likely to induce artifactual effects in the animals under study as well as in the recordings themselves. The findings of early studies may be discounted because of such use. On the other hand, EEG measurements done after completion of RFR exposure may be less definitive because of interpretation problems stemming from the time consumed in attaching the electrodes and the variability in their placement. Moreover, any transient effects that may occur during RFR exposure would disappear when exposure ceases. These points are applicable to the negative findings of Kaplan et al. (1982).

In several studies, such as by Tyazhelov et al. (1977) and Chou and Guy (1979a), endeavors were made to minimize artifact occurrence by design of electrodes and leads from materials having high resistivities comparable to those for tissue. When such electrodes were implanted prior to exposure and were present during exposure, no significant differences in EEGs or evoked responses between control and RFR-exposed animals were obtained, as exemplified by the study of Chou et al. (1982).

3.4.4 CALCIUM EFFLUX

It has been reported in various studies that exposure of samples of brain tissue from newly hatched chickens to 147-MHz or 450-MHz RFR at levels in the range 1-2 mW/cm^2 that were amplitude-modulated at discrete frequencies below about 100 Hz increases the rate of exchange of calcium ions between the tissue and the fluid bathing it (the "calcium-efflux effect"). The maximum effect was seen for modulation at 16 Hz, and no effect was seen for unmodulated 147-MHz or 450-MHz RFR. A similar effect was reported for exposure of the cortex of the paralyzed but awake cat.

Bawin et al. (1975) described the experimental protocol. After each neonate chick was decapitated, its forebrain was quickly excised and each of its cerebral hemispheres was incubated for 30 minutes in a mixture of physiologic medium and saline containing the radiotracer $^{45}Ca^{++}$. After incubation, the samples were washed three times in a solution without the tracer. They were then immersed in physiologic medium for 20 minutes during which one hemisphere of each chick was exposed to RFR, with the other hemisphere as its control. On treatment completion, an aliquot of each bathing solution was processed and assayed for radioactivity by liquid scintillation counting.

The exposures were to a 147-MHz field between two large aluminum plates within an environmental chamber maintained at constant temperature and relative humidity. The field was amplitude-modulated at 0.5, 3, 6, 9, 16, 20, 25, or 35 Hz, or was not modulated. The RFR applied to the plates was adjusted to yield intensities in the range 1-2 mW/cm^2.

The results for the unmodulated field and each modulation frequency were plotted as bar graphs of the mean percentage concentration increases (effluxes) of $^{45}Ca^{++}$ relative to the corresponding mean for unexposed samples, with standard errors of the means (SEs). The unmodulated field and the fields modulated at 0.5, 3, 6, 9, and 16 Hz yielded progressively larger increases in calcium efflux, with a high of 19% (119% of control) for 16 Hz. Calcium efflux for 0 Hz (unmodulated), 0.5 Hz, and 3 Hz were nonsignificant ($p>0.05$); those for 6 and 9 Hz were significant at the 5% level, and those for 11 and 16 Hz were significant at the 1% level. For the frequencies above 16 Hz, calcium efflux progressively declined with increasing frequency: the mean efflux was significant ($p<0.05$) for 20 Hz and was nonsignificant ($p>0.05$) for 25 or 35 Hz.

The effects of RFR exposure on calcium efflux were compared with those from chick brains poisoned with sodium cyanide. Four sets were assayed, each set consisting of five poisoned samples and five normal samples: One set each was tested for the effects of exposure to fields modulated at 0, 0.5, and 16 Hz and one set was tested without RFR exposure.

The results showed that although the mean effluxes from the normal and poisoned brains for 16-Hz modulation were significantly higher than their respective controls, the differences between the poisoned and normal brains for each exposure condition were not significant. The authors stated: "The field effects observed previously were not altered by the cyanide treatment, which strongly suggests that the $^{45}Ca^{++}$ effluxes from the cerebral tissues are independent of any ongoing metabolism." Those results also indicate that no calcium had moved across cell membranes, i.e., that calcium efflux is not an effect involving transmembrane calcium transport.

Bawin and Adey (1976a) performed similar experiments to ascertain whether the previously observed calcium efflux from amplitude-modulated 147-MHz fields was due to the carrier frequency or the modulation itself. They exposed chick-brain preparations to sinusoidal fields at discrete frequencies of 1, 6, 16, or 32 Hz [in the extremely-low-frequency (ELF) and sub-ELF ranges] instead of to 147-MHz fields amplitude-modulated at such frequencies. Exposures were for 20 minutes at peak fields (in air) of 5, 10, 56, and 100 V/m.

The results indicated that the effect with ELF and sub-ELF fields was opposite to that with amplitude-modulated 147-MHz fields: Decreases rather than increases of calcium efflux were obtained for all conditions except with 1 Hz at 10 V/m, with maximum effect for 6 and 16 Hz at 10 V/m. In addition, the data indicated the existence of a field-amplitude "window" (as well as a frequency window). Specifically, the decreases for 6 and 16 Hz were statistically significant at 10 and 56 V/m but not at 5 or 100 V/m.

Regarding their statistical treatment of the data, Bawin and Adey (1976a) presented their rationale for discarding sample counts that were more than 40% above or below the mean of any set of 10 samples, and for excluding extreme counts in any set that were more than 1.5 standard deviations from the mean. Despite the authors' rationale, the validity of discarding extreme values after the fact rather than from prior knowledge that experimental error

may have occurred in those specific samples is questionable, and weakens the credibility of the results.

Sheppard et al. (1979) similarly prepared and exposed chick-brain halves to 450-MHz RFR sinusoidally modulated at 16 Hz only, this being the modulation frequency for maximum effect in prior studies with 147-MHz RFR. Exposures were for 20 minutes in a transverse electromagnetic (TEM) cell (rather than between two parallel plates) at power densities of 0.05, 0.10, 1.0, 2.0, or 5.0 mW/cm^2. After exposure, aliquots of bathing solution were assayed for calcium efflux. The differences in normalized radioactivity between the exposed and control samples were significant for 0.10 and 1.0 mW/cm^2, but not for the higher or lower levels, also showing the existence of an intensity window.

Those authors stated: "With attention to the important experimental steps (consistency in the pH and osmolarity of the physiological solution, and careful rinsing of the brains after incubation with the radioactive solution) it was possible to reduce the occurrence and magnitude of extreme values so that no data points were discarded."

Blackman et al. (1979) performed experiments toward reproducing the 147-MHz results of Bawin et al. (1975). They also used a TEM cell to expose chick-brain samples for 20 minutes, but to 147-MHz RFR instead of 450-MHz RFR. Two series of exposures were done. In one series, power density was held constant at 0.75 mW/cm^2 and the modulation frequencies were 0, 3, 9, 16, and 30 Hz. In the other, the modulation frequency was held constant at 16 Hz and the power densities were 0, 0.5, 0.75, 1.0, 1.5, and 2.0 mW/cm^2. The results seem to confirm the existence of the calcium-efflux effect in excised chick brains, at least for 147-MHz RFR amplitude-modulated at 16 Hz. As indicated by the authors, however, the power density window was narrower than those for modulated 450-MHz RFR and for sinusoidal sub-ELF fields.

Blackman et al. (1985a,b) reviewed their prior work on the effects of fields at frequencies in the range 1-300 Hz on calcium efflux from chick brains. Among the findings were windows of frequency and field intensity within which calcium efflux was enhanced, and outside of which alterations of calcium efflux were nonsignificant. However, Blackman et al. (1985b) subsequently noted that their calcium-efflux changes (enhancements) were opposite in direction to the reductions found by Bawin and Adey (1976b) at frequencies in the same range. They also noted that alternating currents flowing in the walls of the TEM cell exposed their samples to a magnetic component as well as the transverse alternating electromagnetic field, whereas only alternating electric fields were produced by the parallel plates used by Bawin and Adey (1976b). Thus, Blackman and coworkers hypothesized that the magnetic component could influence changes in calcium efflux significantly and suggested that a DC magnetic field such as that of the earth might also have a role.

Accordingly, the exposure apparatus used by Blackman et al. (1985b) consisted of a transmission line that permitted use of an alternating electric field either alone or together with an alternating magnetic field. Also, the transmission line was placed within a pair of large Helmholtz coils oriented to produce a DC magnetic field parallel to the earth's field and thereby

permit local alterations of the magnitude and polarity of the local geomagnetic field (LGF).

Preparation of chick-brain samples was similar to that in previous studies. Also, in an endeavor to keep the procedures invariant, four tubes containing chick-brain-halves were treated concurrently with six tubes containing equivalent dummy loads (10 tubes total) as in Blackman et al. (1980). Field exposures (including sham-exposures) were for 20 minutes at 37 ^{o}C, with the corresponding half-brains held at the same temperature within a water bath. The following series of exposures were performed and the post-treatment assay for $^{45}Ca^{++}$ in each field- or sham-exposed half-brain was normalized to the value for its control half-brain:

(1) Ten tubes were exposed to a 16-Hz electric field alone at 6, 10, or 40 V/m and 10 other tubes were sham-exposed. The exposure at each level and the corresponding sham-exposure comprised a set. Exposure sets for 6 and 40 V/m were done 8 times and sets for 10 V/m 7 times. Also, 8 sets for 40 V/m were repeated 8 months later.

(2) To compare effects of an alternating electric field alone with those of an alternating electromagnetic field, nine sets, each comprised of an exposure to a 16-Hz electric field at 40 V/m and an exposure to a 16-Hz electromagnetic field at 40 V/m, 59.5 nT, were performed.

(3) A similar design was used for determining the possible influence of the LGF (given as 38 μT, presumably at the experimental site). Eight sets were performed, each consisting of two exposures to a 15-Hz, 40-V/m, 59.5-nT field, one with the normal LGF present and the other with the LGF reduced to 19 μT by the Helmholtz coils. Also, the eight sets were repeated one week later.

(4) Sets of exposures to a 30-Hz, 40-V/m, 59.5-nT field were done for several integral and fractional multiples of the LGF, including negative values representing field reversal. Comparison was made of the results for the altered LGF with those of the normal LGF, and some sets were replicated one week later.

Results for series (1) showed nonsignificant differences between field- and sham-exposed sets for any level or for the combined initial and repeated 40-V/m set. By contrast, 16-Hz electromagnetic fields at 6 V/m, 8.9 nT and at 40 V/m, 59.5 nT had enhanced calcium efflux significantly, whereas Bawin and Adey (1976b) had reported significant reduction for a 16-Hz electric field at 10 V/m.

Direct comparison of the results of series (2) for an alternating electric field only versus an alternating electromagnetic field showed that the calcium efflux for the latter was significantly larger than for the former. The authors stated: "The data demonstrate that the AC magnetic component [59.5 nT] must be present in the 6- and 40-V/m fields to induce an enhanced efflux."

About (3) and (4), they stated: "The results demonstrate that a normally effective 15-Hz signal is ineffective when the net density of the LGF is reduced to half the ambient, and an ineffective 30-Hz signal is effective when the net density is changed to .67x or 2.0x ambient but not when it is increased to 1.33x or to 2.185x ambient...increased efflux resulted at LGFs +0.67x ambient and of ±2.0x ambient when compared to the lack of enhancement for ambient conditions...A slight increase in the density of the LGF from -2.0x to -2.185x the ambient was sufficient to remove the enhancement conditions."

The results for the changes in the LGF appear to indicate that the DC geomagnetic field is fundamentally involved in alterations of calcium efflux, but as is evident in the quotation above, the relation between the magnitudes of the LGF changes and the presence or absence of effect, if any, is obscure. Also not clear is the absence of effect in series (1), in which the alternating magnetic field was absent but the LGF was present, since the magnitude of the normal LGF (38 μT) is about 600-fold larger than the alternating magnetic component (59.5 nT rms) used in all series except (1). It seems plausible that the latter would have been swamped by the former. In addition, the negative findings for series (1) do not gainsay the positive findings obtained by Bawin and Adey (1976b) in the absence of an alternating magnetic component.

In a more recent study, Blackman et al. (1991) reported that calcium efflux can be reduced, enhanced, or nullified by appropriately varying the temperature of the chick-brain samples before and during exposure. The authors hypothesized the existence of a temperature-window effect (an effect that occurs only within a narrow temperature range) and suggested that these results could account for the different outcomes (including those of opposite direction of effect) by various researchers.

Shelton and Merritt (1981) investigated whether pulses of RFR at repetition rates comparable to the modulation frequencies used in the chick-brain studies would elicit alterations in calcium efflux from the rat brain. In each experiment, pairs of samples of cerebral hemisphere from euthanized rats were processed together for RFR- and sham-exposure. Each sample was immersed in medium containing $^{45}Ca^{++}$ in a beaker, in which the sample was incubated for 20 minutes at 37 ^{o}C. Then the samples were washed once with medium that was free of $^{45}Ca^{++}$ and were transferred to clean beakers containing radioactivity-free medium for RFR- or sham-exposure. Because the $^{45}Ca^{++}$ concentration could be affected by the extent of tissue washing, the samples in one experiment were washed with radioactivity-free medium five times instead of once.

In four experiments, exposures were for 20 minutes to 20-ms pulses of 1-GHz RFR, 16 pps, a repetition rate analogous to the 16-Hz amplitude modulation used in the chick-brain experiments. The average power densities were 0.5, 1.0, 2.0, or 15 mW/cm^2, selected to search for the reported power-density window. In two other experiments, samples were exposed for 20 minutes to 10-ms pulses, 32 pps, at 1.0 or 2.0 mW/cm^2. Sham-exposures for each experiment were conducted similarly. Four groups each of RFR- and sham-exposed samples comprised the population for each experiment.

In a seventh experiment, samples washed five times instead of once were exposed to 20-ms pulses, 16 pps, at 1.0 mW/cm^2 (or sham-exposed). In an eighth experiment (with samples washed only once), the exposure parameters used were the same, but exposure was interrupted for about 1 minute each after 4, 8, and 12 minutes of exposure, and 0.5-ml aliquots of the incubation medium were taken and assayed for possible time-dependent effects and replaced with fresh medium.

On completion of RFR- or sham-exposure, the radioactivities of the media and tissue samples were assayed by liquid scintillation counting. These authors defined "efflux value" as the ratio of counts per minute (CPM) of the medium to the sum of the CPMs in tissue and medium, an efflux measure that differed from that used by other investigators. The cerebral tissues taken from the 143 rats in the first six experiments yielded no significant differences between any of the mean $^{45}Ca^{++}$ effluxes when RFR-exposed samples were compared with their corresponding sham-exposed control samples. The mean effluxes for RFR- and sham-exposure in the seventh experiment (24 rats, five washings instead of one) also did not differ significantly from one another, but both means were higher than those obtained in the first six experiments. In the eighth experiment (exposure interruption), successive efflux rises were seen at the three interruption intervals, but again the differences in the means for RFR-exposed and sham-exposed samples at corresponding times were not significant.

Thus, the findings of Shelton and Merritt (1981) were negative, but as pointed out by the authors, no direct comparisons can be made between their results and those of the investigators on chick brains discussed previously because in addition to the difference in species, the samples were actually exposed (with a duty factor of 0.32) for only a third of the 20-minute period (at correspondingly higher peak levels), and because the spectral energy distribution for the 16-pps repetition rate differed markedly from that in the sidebands for 16-Hz amplitude-modulated RFR.

Merritt et al. (1982) performed experiments *in vivo* as well as *in vitro* on possible pulsed-RFR-induced alterations of calcium efflux from the rat brain. For both types of experiment, brain tissue was loaded with $^{45}Ca^{++}$ by injection directly into the right lateral ventricle of rats anesthetized with ether.

In the *in vitro* experiments, the rats were euthanized by cervical dislocation after intraventricular injection of $^{45}Ca^{++}$. Six samples of brain tissue excised as in the previous study were concurrently exposed for 20 minutes to 20-ms pulses, 16 pps, of 1-GHz RFR at 1 or 10 mW/cm^2 (SAR 0.29 or 2.9 W/kg) or of 2.45-GHz RFR at 1 mW/cm^2 (SAR 0.3 W/kg), with a like number of samples sham-exposed as controls.

Although the radioactivities of the incubation media and the tissue samples were assayed by liquid scintillation counting, the results were not given in terms of the efflux values as defined in Shelton and Merritt (1981); instead, the mean disintegrations per minute per gram of tissue (DPM/g) and standard deviations (SDs) were presented. By the two-tailed t-test, the difference in the mean DPM/g values between RFR-exposed and sham-exposed samples was not significant for any of the exposure conditions.

For the whole-animal exposures, 2 hours after the rats were injected with $^{45}Ca^{++}$, each rat was gently squeezed between two sides of a holder to keep its body axis constant during exposure, and groups of 12 rats each were exposed for 20 minutes to 2.06-GHz RFR with their long axes parallel to the E-field. One group each was exposed to CW at 0.5, 1.0, 5.0, or 10.0 mW/cm^2 and one group each to 10-ms pulses at 8, 16, or 32 pps and average power density of 0.5, 1.0, 5.0, or 10.0 mW/cm^2 (16 groups total). A 17th group was sham-exposed. By calorimetry with models of the rat, the normalized SAR was 0.24 W/kg per mW/cm^2, yielding 0.12, 0.24, 1.2, and 2.4 W/kg for the average power densities above.

After exposure, the rats were euthanized, and their brains were removed and processed appropriately for $^{45}Ca^{++}$ assays. Statistical tests on the 17 treatment combinations (4x4 RFR exposures, 1 sham-exposure) showed that the difference between the sham group and the combined RFR groups and the differences between the sham group and the individual RFR groups were nonsignificant.

In this paper, as in Shelton and Merritt (1981), an attempt was described to determine whether the changes in calcium efflux reported to be induced in chick brains by *in-vitro* exposure to amplitude-modulated RFR might also be observed in rats given *in-vitro* or *in-vivo* exposure to pulse-modulated waveforms. No RFR-induced calcium-efflux changes were found. However, in addition to the previously noted differences in species, carrier frequency, and waveform, there were other important ones, most notably that loading of the brain with $^{45}Ca^{++}$ was done by injection into the right ventricle of the brain of the intact animal, whereas external bathing media containing $^{45}Ca^{++}$ were used in the other studies.

Adey et al. (1982) presented the results of a study of $^{45}Ca^{++}$ efflux from the cortex of the paralyzed but awake cat. A hole centered over the right cortex was drilled under ether anesthesia. The dura was removed and a plastic well was fitted into the aperture to make gentle contact with the surface of the pia. Nonradioactive physiologic medium was added to the well and all skin incisions and pressure points were anesthetized locally. The use of ether was then discontinued, the cat was paralyzed, and a tracheotomy was used to maintain artificial respiration.

During recovery from ether anesthesia, the fluid level in the well was replaced at 10-minute intervals for 30 minutes, to ensure that the fluid was clear. Incubation was then begun with medium that contained $^{45}Ca^{++}$, and was continued for 90 minutes, at the end of which the fluid was replaced with nonradioactive medium. At 10-minute intervals during the remainder of the experiment, the fluid was exchanged completely with fresh medium, and aliquots of each solution were removed and assayed for $^{45}Ca^{++}$.

Twenty-three female cats were used. Starting at different times after completion of the incubation of the cortex with $^{45}Ca^{++}$, the cats were sham-exposed or exposed individually for 60 minutes to 450-MHz RFR that was amplitude-modulated at 16 Hz, and differences in the efflux patterns were sought at intervals ranging from 80 to 120 minutes. Each cat was placed in a plastic stereotaxic headholder, with its body axis normal to the incident

field and with the right cerebral cortex nearest the RFR source. The average power density was 3.0 mW/cm^2, for which the electric field within the interhemispheric fissure was found to be 33 V/m, corresponding to an SAR of 0.29 W/kg.

The description of the data-analysis methods used was obscure. The authors fitted relative $^{45}Ca^{++}$ efflux data taken at 10-minute intervals in the absence of the RFR by a time-dependent equation involving the sum of two exponential terms. They therefore log-transformed the data and used linear regression to obtain an idealized curve of relative efflux versus time. They then quantified the results for RFR-exposed cats in terms of the means of the relative squared deviations of experimental data from the idealized curve at sampling points (rather than comparing the slope of the regression line for the RFR-exposed cats with the slope of the idealized curve), and similarly for the sham-exposed cats. Presumably this was done because the mean values for the RFR-exposed and sham-exposed cats were comparable, but the standard deviations for the former were larger than for the latter.

Next, the authors paired experimental curves of relative $^{45}Ca^{++}$ efflux (defined in terms of relative squared deviations) versus time from RFR- and sham-exposed cats. Graphed were the data for a representative pair of cats, one exposed to RFR for 60 minutes starting after 90 minutes of pre-exposure measurements, and the other similarly sham-exposed. By eye, the average slopes of the two curves were about the same up to about the first 60 minutes of the pre-exposure measurement period. From about 60 minutes onward, which included the 60-minute interval of RFR- or sham-exposure and afterward, both slopes were smaller, but the average slope for the RFR-exposed cat was less negative than for the sham-exposed cat, and showed cyclic variations ("waves of increased $^{45}Ca^{++}$ efflux") with a periodicity of about 25 minutes.

No experimental data for RFR-exposed and sham-exposed animals were given (other than mention of their use in the curve-fitting method noted above) or were directly compared for statistically significant differences. The absence of such data seemed to imply that the important differences in calcium efflux for the RFR-exposed and sham-exposed animals were in the mean-squared deviations from the ideal and the cyclic variations about the idealized linear fits to the data, and not between the values themselves at corresponding times or their means.

3.4.4.1 SUMMARY

In summary, in studies by Bawin et al. (1975) and Sheppard et al. (1979), calcium efflux was reported to occur in brain hemispheres of newly-hatched chicks that were excised and exposed to 147-MHz or 450-MHz RFR amplitude-modulated at frequencies below about 100 Hz. The exposures were done between a pair of plane-parallel plates. The effect was absent with unmodulated RFR at the same frequencies; it was highest for modulation with 16 Hz, and it exhibited an intensity window in the range 0.10 to 1.0 mW/cm^2, with no effect at higher or lower RFR levels. Other results with cyanide-poisoned chick brains indicated that calcium efflux is not an effect that involves calcium transport across cell membranes.

Bawin and Adey (1976) also performed experiments indicating that the effect was ascribable to the modulation itself rather than to RFR carrier frequency. In those experiments, they exposed chick-brain preparations to sinusoidal fields at discrete frequencies of 1, 6, 16, or 32 Hz instead of to RFR fields amplitude-modulated at those frequencies. However, the effects at the sub-ELF and ELF frequencies were opposite in direction to those for the modulated RFR.

Blackman et al. (1985b) performed similar experiments, but used a TEM (transverse electromagnetic) line for exposure. Currents in the walls of the TEM line yielded an alternating magnetic component in addition to the TEM field, in contrast to the electric field only between the parallel plates used by Bawin and coworkers. This led the authors to theorize that the magnetic component could influence changes in calcium efflux and to suggest that the earth's DC magnetic field might also be involved in the effect. They therefore did exposures in a transmission line that permitted use of an alternating electric field either alone or together with an alternating magnetic field. In addition, they placed the transmission line within a pair of large Helmholtz coils oriented to produce a DC magnetic field, parallel to the earth's field, that could be varied to alter the magnitude and polarity of the local geomagnetic field. Mixed results were obtained, from which it was difficult to relate the occurrence of calcium efflux or its absence to the changes in local geomagnetic field. More recently, Blackman et al. (1991) reported that calcium efflux can be reduced, enhanced, or nullified by appropriately varying the temperature of the chick-brain samples before and during exposure, results the authors interpreted as indicating the existemce of a temperature window analogous to the RFR intensity window.

Shelton and Merritt (1981) investigated whether pulses of RFR at repetition rates comparable to the modulation frequencies used in the chick-brain studies would elicit alterations in calcium efflux from the rat brain. In some experiments, they excised and exposed brain hemispheres from rats for 20 minutes to 20-ms pulses of 1-GHz RFR modulated at 16 pps, at average power densities of 0.5, 1.0, 2.0, or 15 mW/cm^2 selected to search for the reported power-density window; in others, the exposures were to 10-ms pulses, 32 pps, at 1.0 or 2.0 mW/cm^2. The brain hemispheres were then assayed for calcium efflux. Their findings were negative, but as they pointed out, no direct comparisons can be made between their results and those of investigators on chick brains because besides the differences in species and exposure durations, there were important differences between pulse modulation at 16 pps and sinusoidal modulation at 16 Hz.

Merritt et al. (1982) also performed experiments with rats *in vivo*. The brains of rats anesthetized with ether were loaded with $^{45}Ca^{++}$ by injection directly into the right lateral ventricle. Two hours later, the rats were exposed for 20 minutes to 2.06-GHz CW or pulsed RFR with their long axes parallel to the E-field. The average power densities for both the CW and pulsed RFR ranged from 0.5 to 10.0 mW/cm^2. By calorimetry, the corresponding whole-body SARs were 0.12 to 2.4 W/kg. Again, their findings were negative. Similar experiments were done *in vitro*, in which the rats were euthanized after injection with $^{45}Ca^{++}$, followed by excision of the brain hemispheres and their assay for calcium efflux. Once more, no RFR-induced calcium-efflux changes were found.

Adey et al. (1982) exposed paralyzed awake cats for 60 minutes to 450-MHz RFR, amplitude-modulated at 16 Hz, after incubating the brain cortex of each cat with $^{45}Ca^{++}$ through a hole in the skull. The average power density was 3.0 mW/cm^2 (SAR about 0.29 W/kg in the interhemispheric fissure). The authors used the experimental data for curve fitting, but did not present any actual data. Their statistical treatment of the data was obscure, rendering it difficult to interpret the findings.

In conclusion, although researchers in several laboratories have reported obtaining the calcium-efflux effect, researchers in other laboratories have been unable to confirm its existence. Several of the recent studies that report positive findings suggest that magnetic fields, primarily at powerline frequencies (as well as the earth's DC field), contribute significantly to the effect. However, there is no experimental evidence that the effect, if it does exist, would occur in or be harmful to humans or intact animals.

3.5 IMMUNOLOGY AND HEMATOLOGY

Many reports indicate that RFR has specific effects on the immune systems of mammals. Most reported effects were detected after exposure at power densities of about 10 mW/cm^2 and higher; a few effects have been found from exposure to levels as low as about 0.5 mW/cm^2. In most of the studies, the mechanisms for the effects were not investigated, and many of the results were not consistent with one another. Representative studies are discussed in this section under appropriate topics.

3.5.1 IN VITRO STUDIES

Early studies were performed *in vitro* to determine whether exposure to RFR can stimulate lymphocytes (one type of leukocyte or white blood cell) to become lymphoblasts, i.e., active in cell division (mitosis), and to undergo mitosis. In such studies, samples of lymphocytes taken from the body were cultured, then exposed to RFR (or exposed, then cultured), and examined for effects induced by the RFR. Usually, such cells were cultured with a mitogen, an agent that stimulates transformation into lymphoblasts and mitosis. In recent studies, more subtle effects on various types of leukocytes were sought. Also sought were effects of exposure *in vitro* on red blood cells (erythrocytes).

3.5.1.1 LEUKOCYTE STUDIES

Smialowicz (1976) exposed suspensions of mouse-spleen cells to 2.45-GHz RFR at 10 mW/cm^2 (SAR about 19 W/kg) for 1, 2, or 4 hours. Similar suspensions held at 37 ^{o}C (without RFR exposure) for the same durations served as controls. After treatment, specimens were cultured with and without each of four different mitogens. No significant differences were seen between RFR-exposed and control specimens treated for corresponding durations. This was true for specimens not stimulated with mitogen as well as those stimulated with any of the four mitogens. The temperature and percentage viability of specimens right after each treatment were also measured, and no significant

differences were seen between exposed and control samples for each treatment period.

Hamrick and Fox (1977) exposed cultures of rat lymphocytes with and without the mitogen phytohemagglutinin (PHA) to 2.45-GHz RFR at 5, 10, or 20 mW/cm^2 (0.7, 1.4, or 2.8 W/kg) for 4, 24, or 44 hours, and assayed them for lymphoblast transformation by the cellular uptake of tritium-labeled thymidine. The differences in thymidine uptake between mitogen-stimulated cultures and non-stimulated cultures for each RFR level and duration were large, but the differences between the RFR- and control cultures were nonsignificant.

Roberts et al. (1983) exposed human mononuclear leukocyte cultures to 2.45-GHz RFR for 2 hours at 4 W/kg, with no attempt to remove heating due to the RFR. Other cultures were sham-exposed, and untreated cultures were controls. The three groups of cultures were assessed for viability on days 1 through 7 after treatment, and assayed daily for DNA, RNA, and total protein synthesis. The mean viability of all three groups both increased and decreased with time, but the differences among the groups were not significant. Similar results were obtained at 0.5 W/kg and intermediate SARs. There were also no significant differences among the groups in DNA, RNA, and total protein synthesis.

Also assayed for the three groups were: spontaneous production of interferon, influenza-virus-induced production of alpha-interferon, and mitogen-induced production of gamma-interferon. Spontaneous production of interferon did not occur. Most of the virus-induced alpha-interferon was present by 24 hours in the RFR group and the other two groups, with no significant differences among the three groups. The mitogen-induced gamma-interferon, usually produced in 48 to 72 hours, was found in all stimulated cultures by 72 hours, with no significant differences among the groups.

In a later study, Roberts et al. (1987) infected human mononuclear leukocyte cultures with influenza virus and then exposed them to 2.45-GHz RFR, either CW, or pulsed at 60 or 16 Hz (duty cycle 0.5), all at 4 W/kg. Control cultures were sham-exposed. No significant differences due to RFR exposure relative to sham-exposure were found in leukocyte viability of virus-infected cultures or uninfected cultures, or in DNA synthesis from mitogen stimulation.

Lyle et al. (1983) sought effects for 60-Hz-amplitude-modulated 450-MHz RFR at 1.5 mW/cm^2 (SAR not stated) on the toxicity of certain rodent T-lymphocytes (effector cells) against lymphoma cells (target cells) of a specific type. Exposure of specific mixtures of effector and target cells was found to inhibit the mean cytotoxicity obtained in their respective control mixtures by 17-24%. Similar suppression percentages (15-25%) were obtained in assays done in the absence of the RFR but in which the effector cells had been RFR exposed before mixing them with the target cells. The authors surmised that cytotoxicity was due to the action of the RFR on the effector cells. They also found that the mean percentage of cytotoxicity inhibition diminished with elapsed time after exposure.

Those authors also did similar cytotoxicity assays for 450-MHz RFR modulated at 0 (unmodulated), 3, 16, 40, 80, and 100 Hz, and compared the

results with those at 60 Hz. Mean cytotoxicity inhibition was negligible with unmodulated RFR; nonsignificant with 3, 16, and 40 Hz; maximal with 60 Hz; and significant (but smaller) with 80 and 100 Hz, indicating that the effects were due to the amplitude modulation itself.

Sultan et al. (1983a) studied the effects of combined RFR exposure and hyperthermia *in vitro* on the ability of normal B-lymphocytes to cap surface immunoglobulin (I_g) following binding of specific antigen (anti-I_g) molecules. They exposed suspensions of normal mouse B-lymphocytes at 37, 41, and 42.5 ^{o}C to 2.45-GHz CW RFR for 30 minutes at levels in the range 5-100 mW/cm^2 (2.25-45 W/kg). Control suspensions at each temperature were sham-exposed. After either treatment, the cells were incubated at 4 ^{o}C for 10 minutes with fluorescein-labeled goat anti-mouse I_g to permit binding of antibody to surface I_g, and the suspensions were transferred to a 37-^{o}C environment for 9 minutes to allow the antigen-antibody capping to occur. Fluorescence microscopy was then used to test the preparations for capping.

Capping was seen in more than 90% of the cells heat-treated at 37 ^{o}C, but in less than 60% of those treated at 41 ^{o}C, and in less than 5% of those treated at 42.5 ^{o}C. The authors concluded that the mechanisms responsible for inhibition of capping in their experiments are thermal in origin, with no apparent effects of 2.45-GHz CW RFR if RFR-exposed and control samples are held at the same temperature.

Sultan et al. (1983b) reported similar results with suspensions of cells exposed for 30 minutes to 147-MHz RFR amplitude modulated at 9, 16, or 60 Hz. The average power density ranged from 0.1 to 48 mW/cm^2 (0.004-2.0 W/kg). Again, capping inhibition increased with temperature, and no significant differences were obtained between RFR-exposed and control specimens held at the same temperature. The authors also found that for temperatures not exceeding 42 ^{o}C, cytotoxicity and capping returned to normal levels 2 hours after heat treatment.

Cleary et al. (1985) exposed rabbit neutrophils (another type of leukocyte) within a temperature-controlled coaxial exposure chamber to 100-MHz CW RFR for 30 or 60 minutes at electric field strengths ranging from 250 to 410 V/m (120 to 341 W/kg), or for 60 minutes to 100-MHz RFR that was amplitude-modulated at 20 Hz (331 W/kg). For controls, they sham-exposed other samples and kept still others outside the exposure chamber at the same temperature as the sham-exposed samples. Results showed that the viability and phagocytotic ability of the neutrophils were not affected by such RFR exposures, i.e., no significant differences were found among the groups for each exposure regimen. However, the credibility of these negative findings is diminished by the relatively large variabilities among the two control groups in each case, an indication of the possible presence of uncontrolled non-RFR factors.

Kiel et al. (1986) sought effects of RFR on the nonphosphorylating oxidative metabolism of human peripheral mononuclear leukocytes (mostly lymphocytes). They noted that production of active oxygen metabolites is accompanied by the generation of chemiluminescence (CL), and that CL can be enhanced by the addition of luminol and used as a sensitive detector of such effects.

Samples of peripheral blood were collected from human volunteers and the leukocytes were separated, washed, and resuspended. Pairs of aliquots within nitrocellulose tubes were used. In the RFR-exposure experiments, one aliquot of each pair was exposed for 30 minutes to 2.45-GHz CW RFR at 104 W/kg with the sample held at 37 ^{o}C, and the other was held at 37 ^{o}C in an incubator without RFR exposure. Other pairs of aliquots were used similarly for sham-exposure. RFR exposures were done for samples from 9 volunteers, and sham-exposures from 6 volunteers.

Following treatment, half of each sample was used for measuring CL activity, and the other half for determining cell counts and viability. After the addition of luminol at time t=0, CL was monitored at 10-second intervals from t=40 to t=180 seconds and the sum of those values divided by the cell concentration was taken as the total CL for each sample. Results were normalized in terms of a stimulation index (SI) for each treatment, defined as the ratio of the difference between treatment and paired control samples in total CL to the total CL in the control.

The authors noted that the CL variability among the 15 donors was large, but that nevertheless, the CLs for both the RFR-exposed and sham-exposed samples significantly exceeded those of their respective incubator-held controls. However, the difference in mean CL between the RFR-exposed and sham-exposed samples was not significant. The differences between the RFR-exposed or sham-exposed samples and the incubated samples were ascribed by the authors to the slow rate of heating in the incubator; a rise from 22 to 36 ^{o}C in the incubator took 39 minutes.

3.5.1.2 ERYTHROCYTE STUDIES

Studies were directed toward effects of RFR interactions with *in vitro* samples of red blood cells (RBCs) taken from animals or humans. Alterations of cell membrane function, particularly any effects on the movement of sodium ions (Na^{+}) and potassium ions (K^{+}) across the membrane were sought.

In early Eastern European studies, the authors reported increased hemolysis (cell breakdown) and efflux of K^{+} from rabbit RBCs exposed to 1-GHz or 3-GHz RFR at levels as low as 1 mW/cm^{2}. In a subsequent U.S. study, Peterson et al. (1979) heated suspensions of rabbit RBCs conventionally or with 2.45-GHz RFR at 10-140 mW/cm^{2} (46-644 W/kg). Suspension temperatures were monitored continuously, and each suspension was assayed for the loss of hemoglobin (Hb) and K^{+} after either treatment. Higher Hb or K^{+} losses were obtained for RFR-exposed suspensions than for conventionally heated suspensions. However, in all experiments in which RFR- and conventionally-heated RBCs were warmed at the same rate to the same final temperature, both Hb and K^{+} were lost in equal amounts, indicating the thermal basis for the effect.

Those U.S. authors also heated samples of human RBCs to 37 ^{o}C by exposing them to 2.45-GHz RFR at 90 mW/cm^{2} (412 W/kg) for 8 minutes and then maintained them there for 37 minutes by exposure at 30 mW/cm^{2} (137 W/kg). Unlike the results for rabbit RBCs, no significant differences among the groups were obtained in either hemolysis or K^{+} release. Such absence of

hemolysis and K^+ release for human RBCs can be taken as an indication that RFR-induced changes in rabbit blood may not be reflected in similar effects with human blood.

Brown and Marshall (1986) sought nonthermal effects of RFR on growth and differentiation of the murine erythroleukemic (MEL) cell line. They noted that in response to an inducer (HMBA), MEL cells form hemoglobin and exhibit other forms of erythroid differentiation, so they exposed tubes of HMBA-cultured MEL cells for 48 hours to 1.18-GHz RFR at an SAR of 18.5, 36.3, or 69.2 W/kg, with incubation temperature held at 37.4 ^{o}C. Control cultures were held at the same temperature in a water bath.

The growth of exposed and control cultures was compared by measuring the elapsed times for cells to double in number; cell differentiation was compared by counting the percentages of cells stained by a hemoglobin-specific dye and by determining the amounts of hemoglobin produced. The results showed no significant differences in any of the three endpoints between the cultures exposed at each RFR level and their corresponding control cultures. Moreover, the mean values for each endpoint did not vary significantly with RFR level.

3.5.2 IN VIVO STUDIES: EFFECTS OF EXPOSURES ON IMMUNOLOGICAL PARAMETERS

Studies of immunological effects of RFR *in vivo* can be divided into those in which changes in specific immunological parameters were sought, the subject of this section, and those in which effects of RFR on the health of the subjects and their resistance to disease were examined, discussed in the next section.

Huang et al. (1977) exposed groups of hamsters for 15 minutes per day, on 5 consecutive days, to 2.45-GHz RFR at levels in the range 5-45 mW/cm^2 (2.3-20.7 W/kg). Blood samples were drawn one hour after exposure and cultured with or without the mitogen PHA. For cultures not stimulated with PHA, a graph of the percentage of transformed cells versus RFR level resembled an inverted U, indicating rises with increasing RFR level to a maximum at 30 mW/cm^2 (13.8 W/kg), followed by a gradual return to control values. The rise in response to the maximum appears to have been thermally based, but the mechanisms for the decreases in response at still higher RFR levels is obscure. The cell counts at blood collection time showed no net lymphocyte increases from other sources such as the lymph nodes or spleen. There were also no significant changes in differential leukocyte counts, thus supporting the contention that RFR does not cause lymphocytosis.

For PHA-stimulated cultures, the authors found that the mean value of Mitotic Index (the percentage of cells in mitosis relative to the total number of lymphocytes) was 3% for controls but diminished significantly for the groups exposed at 30 and 45 mW/cm^2 (13.8 and 20.7 W/kg). A point of interest is that the scatter of values, which was large for the controls, decreased rapidly with increasing RFR level, tending to further confirm that RFR inhibits mitogen-stimulated mitosis. Even at 5 mW/cm^2 (2.3 W/kg), the scatter was still sizable but smaller than for controls, an indication of the thermal basis for the effect.

Huang and Mold (1980) exposed mice to 2.45-GHz RFR at 5-15 mW/cm^2 (3.7-11 W/kg) 30 minutes per day for 1 to 17 days, after which spleen cells were cultured with or without a T-lymphocyte mitogen or a B-lymphocyte mitogen. The radiotracer tritiated thymidine was added during culturing. After culturing, the cells were assayed for thymidine uptake, a measure of DNA synthesis during cell proliferation.

Plots of thymidine uptake versus exposure duration showed responses that varied cyclically with time for cells from both mitogen-stimulated and nonstimulated cultures. However, similar plots for sham-exposed mice also showed cyclical fluctuations, apparently due to factors other than RFR. Therefore, whether RFR per se has cell-proliferative effects could not be ascertained in this study. In another part of the study, exposure at 15 mW/cm^2 (11 W/kg) for 5 days (30 minutes per day) did not diminish the cytotoxic activity of lymphocytes on leukemic cells injected after, or concurrently with, the last exposure.

Lin et al. (1979) exposed mice to 148-MHz RFR at 0.5 mW/cm^2 (0.013 W/kg) for 10 weeks beginning on postpartum day 4, 5, 6, or 7. Control mice were sham-exposed. The exposed and control mice were weighed daily during the exposure period, and then weekly up to age 600 days. The mean weights of the two groups at corresponding times did not differ significantly. Blood was drawn at ages 28 and 70 days (4 and 10 weeks) and at ages 100, 250, 300, 360, and 600 days. No significant differences were found between the RFR and control groups for hematocrit, hemoglobin, leukocyte counts, erythrocyte counts, or differential blood-cell counts.

Wiktor-Jedrzejczak et al. (1977) exposed mice to 2.45-GHz RFR at 14 W/kg in a single 30-minute session or in three such sessions, one per day, three days apart. Control mice were sham-exposed. After exposure, the numbers of T-lymphocytes and B-lymphocytes in the spleens of the two groups were compared. The total T-lymphocyte population was unaffected by either the single-session or triple-session exposures. However, single sessions significantly increased the population of one subclass of B-lymphocytes (complement-receptor-positive, or CR^+) but not of another B-lymphocyte subclass (immunoglobulin-positive, or Ig^+), whereas the triple-session exposures yielded increases in both B-lymphocyte subclasses.

Next, spleen cells from RFR-exposed and sham-exposed mice were cultured with various T-cell or B-cell mitogens, and the numbers of cells in lymphoblastic transformation were determined. Both single and triple exposures resulted in significant increases in blastic transformation of B-cells but nonsignificant effects on T-cells.

Last, mice were inoculated with the antigen SRBC (sheep red blood cells) that induces production of antibodies by B-cells if T-cells are also present, or with another antigen (DNP-lys-Ficoll) that does not require the presence of T-cells for antibody production by B-cells. The mice were then given triple-session RFR- or sham-exposures, after which their spleens were assayed for antibody production. Antibody production in response to either antigen was reduced by the RFR exposure, but only the difference for SRBC was statistically significant. Taken together, the results of this study show

that thermogenic RFR levels (e.g., 14 W/kg) can have weak stimulatory effects on splenic B-lymphocytes but none on T-lymphocytes.

Sulek et al. (1980) found that the threshold for increases in CR^+ B-cells was about 5 W/kg for 30-minute exposures to 2.45-GHz RFR, yielding an energy-absorption threshold of 10 J/g. They also found that multiple exposures at levels below the threshold were cumulative if done within one hour of one another, but not if spaced 24 hours apart, even if the sum of the energy-absorption values exceeded the threshold.

Schlagel et al. (1980) presented results indicating that RFR-induced increases in CR^+ B-cells depend on genetic factors: Strains of mice having the histocompatibility $H\text{-}2^k$ haplotype (e.g., CBA/J) showed marked increases in CR^+ cells due to RFR exposure, whereas those bearing $H\text{-}2^a$, $H\text{-}2^b$, and $H\text{-}2^d$ haplotypes did not. Moreover, $H\text{-}2^k$ mice without a thymus (the source of T-lymphocytes) responded similarly to RFR exposure, showing that the effect was not regulated by the T-cell population.

Wiktor-Jedrzejczak et al. (1981), noting the genetic control over the increases in CR^+ cells found by Schlagel et al. (1980), suggested that the effect might be mediated by a humoral factor. To test that suggestion, they performed experiments involving implantation of spleen cells derived from RFR-exposed CBA/J mice into sham-exposed CBA/J mice and vice versa, and assayed both groups for circulating CR^+ spleen lymphocytes. For either the donor or recipient mice exposed to RFR, the mean frequencies of CR^+ cells were significantly higher than their respective mean control values, thus supporting the hypothesized existence of a humoral factor and showing that the effect is not due to RFR-induced alterations of CR^+ lymphocyte circulation patterns.

Smialowicz et al. (1981a) exposed CBA/J mice 10-12 weeks old to 2.45-GHz CW RFR at 15-40 mW/cm^2 (11-29 W/kg) once for 30 minutes in an anechoic chamber with ambient temperature held constant at 22 ^oC. (The authors noted that mice exposed at 40 mW/cm^2 were under thermal stress and that exposure for 60 minutes at this level was lethal.) Six days later, the percentages of CR^+ spleen cells and the numbers of nucleated spleen cells were determined. The differences in these two endpoints between sham-exposed mice and mice exposed at any of the RFR levels were not significant. Thus, these authors could not confirm the RFR-induced CR^+ increases found by Wiktor-Jedrzejczak and coworkers.

The authors, assuming that older mice may be more responsive, also exposed mice 14, 16, and 24 weeks old at 30 or 40 mW/cm^2 for 30 minutes. Relative to sham-exposed controls, only the 16-week-old mice exposed at 40 mW/cm^2 (29 W/kg) showed significantly higher percentages of CR^+ cells and smaller numbers of nucleated spleen cells. The authors suggested that the internal SAR distributions in mice exposed in their anechoic chamber were considerably different than for mice exposed at the same whole-body SARs in the waveguide used by Wiktor-Jedrzejczak and coworkers.

Liburdy (1979) exposed mice for 15 minutes to 26-MHz RFR at 80 mW/cm^2. This RFR level produced core-temperature rises of 2-3 ^oC, and was called "thermogenic" by the author. The corresponding whole-body SAR was 5.6 W/kg.

For comparison, other mice were heated in an oven at 63 ^{o}C for the same period to obtain the same rises in core temperature.

Lymphopenia (decrease in lymphocyte count) and neutrophilia (rise in neutrophil count) were seen in the RFR-exposed mice, which persisted for about 12 hours after exposure. Those effects could be sustained and the recovery period prolonged by more RFR exposures at 3-hour intervals. By contrast, the oven-heated mice exhibited only slight effects. Injection of a corticosteroid as a positive control yielded a similar time course for lymphopenia and neutrophilia but it also led to a decrease in the total leukocyte population. The effects were absent for mice exposed to 26-MHz RFR at 50 mW/cm^2 or to 5-MHz RFR at 800 mW/cm^2, called "nonthermogenic" RFR, both of which yielded a whole-body SAR of 0.36 W/kg (about the same as the basis for the 1982 ANSI standard) or about 1/16 of the SAR used previously.

Smialowicz et al. (1981b) exposed 16 rats almost continuously for 69-70 consecutive days to 970-MHz RFR at 2.5 W/kg. Another group of 16 rats was similarly sham-exposed. Blood samples were taken from eight rats of each group on day 69, after which their spleens were removed. The other rats were treated similarly on day 70.

There were no significant differences between RFR-exposed and sham-exposed rats in erythrocyte count, total or differential leukocyte counts, mean cell volume of erythrocytes, hemoglobin concentration, or hematocrit. Spleen cells removed from RFR-exposed and sham-exposed rats and cultured with various mitogens exhibited no significant differences in responses. However, blood-serum analysis yielded significantly higher concentrations of triglyceride, albumin, and total protein for the RFR group. The higher albumin and protein concentrations were within the normal ranges for the rat strain used and were not consonant with the absence of changes in erythrocyte assays, indicating that the rats may have been dehydrated.

The authors noted that an SAR of 2.5 W/kg is about half the basal metabolic rate of an adult rat, and they suggested that the increases in triglyceride level may have been due to thermal stress induced by RFR exposure. At 970 MHz, there probably were regions within the rat where local SARs were much higher than 2.5 W/kg, and such higher SARs could have affected the endocrinologic system of the rat.

Smialowicz et al. (1982a) exposed pregnant mice to 2.45-GHz RFR at 28 mW/cm^2 (16.5 W/kg) for 100 minutes daily from gestation day 6 to day 18. At 3 and 6 weeks of age, the pups were assessed for development of primary immune response to the antigen SRBC, proliferation of lymphocytes *in vitro* by stimulation with mitogens, and *in vitro* activity of natural killer (NK) cells against lymphoma cells. No consistent significant differences were found between RFR-exposed and sham-exposed mice in any of the endpoints.

Smialowicz et al. (1982b) exposed mice to CW or pulsed 425-MHz RFR at SARs up to 8.6 W/kg. No differences were seen in mitogen-stimulated responses of lymphocytes or in primary antibody response to sensitization with SRBC or another antigen (PVP) between RFR-exposed and sham-exposed mice, or between mice exposed to the CW or pulse-modulated RFR.

Smialowicz et al. (1983) exposed groups of mice for 1½ hours per day on nine consecutive days to 2.45-GHz RFR at several levels. For positive controls, other mice were injected with either hydrocortisone or saline. Splenic cells were then assayed *in vitro* for NK-cell activity by their cytotoxicity against mouse-lymphoma cells. Significant suppression of NK-cell activity was seen for 30 mW/cm^2 (21 W/kg), but such activity returned to normal within 24 hours after the last RFR exposure. However, this transient effect was not seen at 15 or 5 mW/cm^2 (10.5 or 3.5 W/kg).

NK-cell activity was also assayed *in vivo*. Suppression of activity was seen in mice exposed at 30 mW/cm^2, but with return to normal several days after the last exposure. Hydrocortisone injection caused activity suppression both *in vitro* and *in vivo*.

Ortner et al. (1981) exposed groups of rats to 2.45-GHz RFR for 8 hours at 2 or 10 mW/cm^2 (0.44 or 2.2 W/kg). A sham-exposed group served as controls. Within 5-15 minutes after treatment, peritoneal mast cells were extracted from rats of each group, and mitogen-induced histamine releases therefrom were determined. The results showed no significant differences among the three groups in percentage of cell viability, percentage of cells, amount of histamine per cell, and cell diameter.

For groups of rats similarly exposed, the total red and white cell counts were not affected by 8-hour exposure at either RFR level, nor were blood-hemoglobin levels or percentages of lymphocytes and neutrophils relative to those of the sham group. The other types of cells were also unchanged by the RFR. Serum biochemistry parameters were not affected by either RFR level.

Wong et al. (1985) noted that relatively few studies had been done in the HF band (3-30 MHz), that most such studies showed that thermogenic levels of RFR were necessary for significant effects of acute exposure, and that possible effects of prolonged exposure to low RFR levels in that frequency range were not investigated. Toward the latter purpose, they conducted two experiments with rats at 20 MHz.

In the first experiment, 200 rats were caged in 40 groups of 5 rats. Twenty of the groups were exposed to 20-MHz RFR at 1,920 mW/cm^2 (about 0.3 W/kg) for 6 hours per day, 5 days per week, and the other 20 groups were sham-exposed as controls. After 8 days of treatment, 6 groups each of exposed and control rats were euthanized and examined for histopathology. This was also done for 7 groups each after 22 days and for the remaining 7 groups each after 39 days.

In the second experiment, 24 rats were divided into exposed and control groups of 12 each, but each rat was housed separately and all rats were euthanized after 6 weeks. On termination of the rats, blood samples were collected and the routine counts and blood-chemistry assays were done. The spleens were excised and weighed, and suspensions of spleen cells were prepared. Various other tissues were also examined for histopathology.

The first experiment yielded a significantly higher mean RBC count and a significantly lower mean hemoglobin content for the rats terminated after 39 days of exposure than for the control group, but the statistical analysis

showed that those differences were not RFR-related. In the second experiment, however, no significant differences were seen in RBC count, hemoglobin, or any of the blood-chemistry parameters.

Regarding histopathology, the authors noted that rats examined for quality control before the start of the first experiment were normal, but by day 8, pulmonary congestion and edema, rhinitis, and peribronchiolar and pulmonary perivascular lymphoid proliferation were evident. In addition, emphysema and incomplete lung expansion were present in some rats killed on day 22. However, no pattern of lesions could be attributed to the RFR exposure. Focal disseminated pneumonia was present in four exposed and four control rats of the first experiment euthanized on day 39, but of the 200 rats used in that experiment, only one had any clinical symptoms of illness. All 24 rats in the second experiment were histologically normal at the end of the 6-week period of exposure.

3.5.3 IN VIVO STUDIES: EFFECTS OF CHRONIC EXPOSURE ON HEALTH, LONGEVITY, AND RESISTANCE TO DISEASE

Relatively few investigations have been done to determine whether chronic RFR exposure affects the general health or longevity of animals, or whether such exposure alters resistance to diseases accidentally acquired or purposely administered to animals, or affects severity of such diseases. Representative examples of such investigations follow.

Prausnitz and Susskind (1962) exposed 200 male mice in groups of 10 for 4.5 minutes per day, 5 days per week, for 59 weeks to 9.3-GHz pulsed RFR at 100 mW/cm^2 average power density (roughly 45 W/kg). Exposures of that duration yielded a mean rise in body temperature of 3.3 ^{o}C. For a test group, the rise that caused death in 50% of the mice (LD_{50}) was 6.7 ^{o}C, attained in 12 minutes at 100 mW/cm^2. Thus, exposure for 4½ minutes at 100 mW/cm^2 was sublethal. Controls were 100 sham-exposed mice.

Some deaths occurred in both groups during the exposure series and were attributed to a pneumonia infection introduced accidentally into the colony during the experiment. However, the death rate was found to be lower in the RFR-exposed mice than in the sham-exposed mice: On series completion, 65% of the RFR-exposed mice and only 50% of the control mice were still alive. The authors ascribed the better survival of the exposed mice to the protective effect of the daily rise in temperature ("fever") induced by the RFR. That explanation seems plausible, but was not proven. Among the results of tissue examination were liver abscesses in some mice, but because of tissue breakdown (autolysis), the relative incidence in RFR-exposed and control mice could not be determined.

The authors reported that some mice had developed leukosis [also spelled leucosis], which they described as a "cancer of the white blood cells," and that leukosis incidence was higher in the exposed mice than the control mice. This effect was real but the interpretation by the authors was probably faulty. In dictionaries of medicine and pathology, leukosis is defined as an abnormal rise in the number of circulating white blood cells, and is not regarded as a form of cancer. Various factors can give rise to

leukosis, including stress, disturbances of the endocrine system, and infection such as pneumonia. The stated presence of pneumonia in the mouse colony may have caused the observed liver abscesses.

Roberts and Michaelson (1983) reanalyzed the data of Prausnitz and Susskind (1962) with appropriate statistical treatment. They found that the results do not support a link between exposure to RFR and cancer development. They also remarked that the greater longevity of the RFR-exposed mice could be taken equally plausibly as indicating that the RFR was beneficial.

Szmigielski et al. (1980) exposed mice to CW or pulsed 2.45-GHz RFR at 5 or 15 mW/cm^2 (2-3 or 6-9 W/kg) 2 hours per day for 6 or 12 weeks prior to injecting the mice with staphylococcal bacteria at a dose selected to yield a 3-day post-injection survival rate of 60% for control mice. For the mice exposed at 5 mW/cm^2 for 6 weeks before injection, the survival rate was 80%. For those exposed at the same RFR level for 12 weeks, the survival rate was 45%. The differences among the two RFR groups and the control group were not statistically significant. The survival rates for those exposed at 15 mW/cm^2 for 6 or 12 weeks were 25% and 5%, respectively.

Liddle et al. (1987) sought effects of exposure to RFR at various ambient temperatures on the survival of mice given an LD_{50} dose of another strain of staphylococcus. They injected mice with that staphylococcus strain and exposed them to 2.45-GHz RFR at 10 mW/cm^2 (6.8 W/kg) for 5 days (4 hours per day) at 8 ambient temperatures in the range 19-40 ^{o}C and 50% relative humidity. Equal numbers of mice were injected with staphylococcus and sham-exposed.

In the temperature range 19-31 ^{o}C, the percentages of RFR-exposed mice that survived the staphylococcus challenge were significantly higher than for the corresponding sham-exposed mice. Above 31 ^{o}C, the survival values of the RFR-exposed mice dropped sharply, to 0% at 37 ^{o}C. Similar results were seen for the sham-exposed mice above 34 ^{o}C; survival dropped to 0% at 40 ^{o}C. The results also indicated that most of those deaths were due to hyperthermia, and showed that exposure to RFR may be beneficial to infected animals at low and moderate ambient temperatures, in consonance with the findings of several other studies.

In the University of Washington study discussed in Section 3.2.3, a group of 100 male rats was exposed unrestrained to 2.45-GHz RFR at average power density about 0.48 mW/cm^2 in individual cylindrical waveguides under controlled-environmental and specific-pathogen-free conditions. Another group of 100 male rats was similarly sham-exposed. Exposures were begun at age 8 weeks and continued for 25 months. At 13 months, 10 each of the RFR-exposed and sham-exposed rats were euthanized (the interim kill), as were 10 of the 12 RFR-exposed and 10 of the 11 sham-exposed rats that survived the 25-month regimen.

Suspensions of splenic cells were assayed for populations of T-cells and B-cells, complement-receptor-positive (CR^+) cells, and plaque-forming cells in response to immunization with sheep red blood cells (SRBC) or to saline for comparison. Also, such suspensions were stimulated with various

mitogens, and the stimulation index relative to unstimulated cultures was determined.

The results for the interim kill showed significantly higher counts of splenic T-lymphocytes and B-lymphocytes for the RFR-exposed rats than the sham-exposed rats, indicating that the RFR had stimulated the lymphoid system. By contrast, however, there were no significant differences in T-cell and B-cell populations between the RFR and sham groups of the terminal kill, a possible indication of the onset of immunosenescence.

The CR^+ values for the RFR groups of both the interim and terminal kills were lower than for the sham groups, but the differences were not significant, indicating no differences between RFR and sham groups in lymphocyte maturation. The percentages of plaque-forming cells for the SRBC-immunized rats was nonsignificantly higher for the RFR group than the sham group in the interim kill, but was nonsignificantly lower in the terminal kill.

The mitogen-stimulation results for the RFR group of the interim kill showed higher responses than the sham group to T-cell mitogens PHA and Con A, but only the difference for Con A was significant. The responses of the RFR-exposed group to the B-cell mitogens LPS and PPD were respectively significantly higher and lower than for the sham-exposed group. The RFR group also yielded a significantly higher response to nonspecific mitogen pokeweed (PWM) than the sham group. No mitogen-stimulation results could be obtained for the terminal kill because the lymphocyte cultures failed to grow and respond to any of the mitogens.

Blood samples drawn periodically from all of the rats were analyzed. The samples were taken under light anesthesia to avoid stress-induced corticosterone elevation. The first samples were drawn 4 weeks before the start of the exposure regimen to provide baseline data. The other samples were taken after 7 weeks of exposure, then at subsequent 6-week intervals during the first year of exposure, and at 12-week intervals during the second year of exposure. However, the numbers of rats sampled decreased with time because of the withdrawals and mortality.

The blood samples were assayed for various hematologic parameters and serum chemistry. By multivariate analyses, there were no overall significant differences between the RFR-exposed and sham-exposed rats in the hematologic parameters. Differences in thyroxine (T_4) levels between the RFR-exposed and sham-exposed rats were nonsignificant, indicating that the RFR had no effect on the hypothalamic-pituitary-thyroid feedback mechanism. As expected, however, the T_4 levels of both groups decreased significantly with age.

Overall, the results of periodic behavioral test sessions showed no significant differences between the RFR-exposed and sham-exposed rats at corresponding times. However, as discussed in Section 3.2.3, primary malignant lesions of several types were found in both groups, but the numbers of rats that had each type of malignancy were similar to those reported in the literature for untreated rats of the same strain, and the differences in numbers of rats for each specific type of malignancy were all statistically nonsignificant.

There were totals of 18 rats with malignancies in the RFR group and 5 rats in the sham group, a difference noted by the authors to be statistically significant. Little credence can be given to this point because of the nonsignificant differences for each malignancy type and because combining those nonsignificant differences to attain statistical significance is an oncologically dubious procedure. Also, the results of the study showed no significant differences between RFR and sham groups in the incidence of benign tumors, a point of importance if the initiation process is assumed to be similar for both benign and malignant tumors.

The authors stated: "The finding here of excessive malignancies in the exposed animals is provocative; however, when this single finding is considered in light of other parameters evaluated, it is questionable if the statistical difference reflects a true biological activity".

Toler et al. (1988) implanted cannulas in the aortas of 200 male white rats. After the rats recovered, 100 of them were concurrently exposed to 435-MHz pulsed RFR (1-μs pulses at 1,000 pps) in a special facility, described by Bonasera et al. (1988). The facility consisted of four circular parallel-plate waveguides stacked vertically. Each such waveguide radiated horizontally outward in the TE_{10} mode (with horizontal polarization). Placed around the periphery of each waveguide were 25 rats in individual cages that permitted unfettered movement.

Exposures were at 1 mW/cm^2 average power density for about 22 hours daily, 7 days a week, for 6 months. Because of rat movements, the whole-body SARs varied with time, ranging from 0.04 to 0.4 W/kg, with a mean of about 0.3 W/kg. An identical stack of waveguides was used for concurrent sham-exposure of the other 100 rats.

Small samples of blood were drawn cyclically without rat restraint or anesthesia and assayed for the stress hormones ACTH, corticosterone, and prolactin in the plasma; for plasma catecholamines; and for hematologic parameters, including hematocrit and various blood cell counts. Also monitored were heart rates and arterial blood pressure. Results showed no significant RFR-induced differences between groups in any of the endpoints.

3.5.4 SUMMARIES ON IMMUNOLOGY AND HEMATOLOGY

3.5.4.1 STUDIES IN VITRO

Smialowicz (1976) compared suspensions of mouse-spleen cells exposed to 2.45-GHz RFR at 10 mW/cm^2 (19 W/kg) for up to 4 hours with suspensions held at 37 ^{o}C for the same durations as controls. Following treatment, suspensions were cultured with or without each of four different mitogens. No significant differences in percentages of cells undergoing mitosis or percentages of viable cells were found between RFR-exposed and control specimens treated for corresponding durations. Hamrick and Fox (1977) also obtained negative results for rat lymphocytes cultured with or without the mitogen PHA and exposed to 2.45-GHz RFR at up to 20 mW/cm^2 (2.8 W/kg) for up to 44 hours.

Roberts et al. (1983) found the viability of cultures of human mononuclear leukocytes to be unaffected by exposure to 2.45-GHz RFR for 2 hours at SARs in the range 0.5 to 4 W/kg. There were also no significant effects on DNA, RNA, and total protein synthesis, or in assays for spontaneous production of interferon, influenza-virus-induced production of alpha-interferon, and mitogen-induced production of gamma-interferon. In a later study, Roberts et al. (1987) infected human mononuclear leukocyte cultures with influenza virus and then exposed them to 2.45-GHz RFR, either CW or pulsed at 60 or 16 Hz, all at 4 W/kg. Control cultures were sham-exposed. No significant differences due to RFR exposure relative to sham-exposure were found in leukocyte viability of virus-infected cultures or uninfected cultures, or in DNA synthesis from mitogen stimulation.

Lyle et al. (1983) sought effects for 60-Hz-amplitude-modulated 450-MHz RFR at 1.5 mW/cm^2 (SAR not stated) on the effectiveness of a specific class of rodent T-lymphocytes against a specific class of lymphoma cells. Mixtures of T-lymphocytes and lymphoma cells exposed to the RFR showed reductions of 17-24% in mean effectiveness of the former against the latter relative to unexposed mixtures. Similar percentages (15-25%) were obtained in mixtures not exposed to the RFR but in which T-lymphocytes were exposed to RFR before mixing them with lymphoma cells, thus indicating that the effect of the RFR was on the T-lymphocytes. However, the effect on the T-lymphocytes decreased with elapsed time after exposure. Effects were also sought for 450-MHz RFR modulated at 3, 16, 40, 80, and 100 Hz. The effect was negligible with unmodulated RFR; nonsignificant with 3, 16, and 40 Hz; maximal with 60 Hz; and significant (but smaller) with 80 and 100 Hz, an indication that the effects were due to the amplitude modulation itself.

Sultan et al. (1983a) studied the effects of combined RFR exposure and hyperthermia on the effectiveness of normal mouse B-lymphocytes against a specific antigen (anti-mouse immunoglobulin from the goat). They exposed suspensions of normal mouse B-lymphocytes at 37, 41, and 42.5 ^{o}C to 2.45-GHz CW RFR for 30 minutes at levels in the range 5-100 mW/cm^2 (2.25-45 W/kg). Control suspensions at each temperature were sham-exposed. The effectiveness of B-lymphocytes against the antigen was more than 90% for cells heat-treated at 37 ^{o}C, but less than 60% of those treated at 41 ^{o}C, and less than 5% of those treated at 42.5 ^{o}C. The authors concluded that the mechanisms involved are thermally based, with no apparent effects of the RFR per se if RFR-exposed and control samples are held at the same temperature.

Sultan et al. (1983b) reported similar negative findings with cell suspensions exposed for 30 minutes to 147-MHz RFR amplitude-modulated at 9, 16, or 60 Hz at average power densities from 0.1 to 48 mW/cm^2 (0.004-2.0 W/kg). Thus, their results showed no amplitude-modulation effect. They also found that for temperatures not exceeding 42 ^{o}C, the effectiveness of mouse B-lymphocytes returned to normal 2 hours after heat treatment.

Cleary et al. (1985) obtained negative findings on the viability and phagocytotic ability of rabbit neutrophils exposed to 100-MHz CW RFR for 30 or 60 minutes at electric field strengths ranging from 250 to 410 V/m (120 to 341 W/kg), or for 60 minutes to 100-MHz RFR amplitude-modulated at 20 Hz (331 W/kg). However, the credibility of these findings is diminished by the

relatively large variabilities among the control groups in each case, an indication of the possible presence of uncontrolled non-RFR factors.

Kiel et al. (1986) sought effects of RFR on oxidative metabolism of human peripheral mononuclear leukocytes. They noted that chemiluminescence (CL) occurs in the production of oxygen metabolites and that CL can be enhanced and used as a sensitive detector of such effects. They collected blood samples from human volunteers, and separated, washed, and resuspended the leukocytes. Samples were paired, and one of each pair was exposed for 30 minutes to 2.45-GHz CW RFR at 104 W/kg with the sample held at 37 ^{o}C and the other was held at 37 ^{o}C in an incubator without RFR exposure. After treatment, half of each sample was used for measuring CL activity, and the other half for determining cell counts and viability. The differences between the RFR-exposed and sham-exposed samples were not significant.

In studies of possible effects of RFR interactions with samples of red blood cells (RBCs) taken from animals or humans, alterations of cell membrane function, particularly any effects on the movement of sodium ions (Na^{+}) and potassium ions (K^{+}) across the membrane were sought. In early studies done in Eastern Europe, increases in cell breakdown and efflux of K^{+} from rabbit red blood cells (RBCs) were reported for exposure to 1-GHz or 3-GHz RFR at levels as low as 1 mW/cm^{2}. Peterson et al. (1979) found that heating suspensions of rabbit RBCs with 2.45-GHz RFR at 10-140 mW/cm^{2} (46-644 W/kg) yielded higher Hb or K^{+} losses than conventionally heating suspensions. However, in all experiments in which RFR- and conventionally-heated RBCs were warmed at the same rate to the same final temperature, both Hb and K^{+} were lost in equal amounts, indicating the thermal basis for the effect. On the other hand, Peterson et al. (1979) used 2.45-GHz RFR to heat samples of human RBCs to 37 ^{o}C and maintain them there, and found no significant differences in either hemolysis or K^{+} release relative to conventionally heated samples.

Brown and Marshall (1986) sought nonthermal effects of RFR on growth and differentiation of the murine erythroleukemic (MEL) cell line. They exposed MEL cells cultured with HMBA, a substance that induces MEL cells to differentiate and form hemoglobin, to 1.18-GHz RFR at SARs up to 69.2 W/kg, with incubation temperature held at 37.4 ^{o}C. There were no significant differences in any of the endpoints between cultures exposed at each RFR level and their corresponding control cultures.

3.5.4.2 STUDIES IN VIVO

In summary of the studies on immunological parameters *in vivo*, Huang et al. (1977) exposed hamsters to 2.45-GHz RFR at levels in the range 5-45 mW/cm^{2} (2.3-20.7 W/kg), and cultured leukocyte suspensions with or without the mitogen PHA. For unstimulated cultures, the percentage of transformed cells rose with RFR level to a maximum at 30 mW/cm^{2} (13.8 W/kg), a thermal effect. For obscure reasons, however, the percentage of transformed cells decreased at still higher RFR levels. There were no significant changes in differential leukocyte counts, thus supporting the contention that RFR does not cause lymphocytosis. For PHA-stimulated cultures, the percentage of cells in mitosis relative to the total number of lymphocytes diminished significantly for exposure at 30 and 45 mW/cm^{2} (13.8 and 20.7 W/kg).

Huang and Mold (1980) exposed mice to 2.45-GHz RFR at 5-15 mW/cm^2 (3.7-11 W/kg), after which spleen cells were cultured with the radiotracer tritiated thymidine and with or without a T-lymphocyte mitogen or a B-lymphocyte mitogen. After culturing, the cells were assayed for thymidine uptake, a measure of DNA synthesis during cell proliferation. The results for the RFR-exposed mice showed cyclic variations of thymidine uptake with time for mitogen-stimulated and nonstimulated cultures, but also for the sham-exposed mice apparently due to factors other than RFR, thus rendering the findings of this study questionable.

Lin et al. (1979) exposed mice to 148-MHz RFR at 0.5 mW/cm^2 (0.013 W/kg) for 10 weeks beginning on postpartum day 4, 5, 6, or 7, and weighed them periodically up to age 600 days. The mean weights of the mice did not differ significantly from those of sham-exposed mice at corresponding ages. Blood samples drawn periodically up to age 600 days showed no significant differences in any of the blood parameters from those of sham-exposed mice.

Wiktor-Jedrzejczak et al. (1977) exposed mice to 2.45-GHz RFR at 14 W/kg in a single 30-minute session or in three such sessions, one per day, three days apart. After exposure, the numbers of T-lymphocytes and B-lymphocytes in the spleens were compared with those for sham-exposed mice. Total T-lymphocyte populations were unaffected by either single-session or triple-session exposures. However, single sessions significantly increased the population of one subclass of B-lymphocytes (CR^+) but not of another subclass (Ig^+), whereas triple sessions increased both subclasses. Also, spleen cells from mice given single or triple exposures and cultured with various T-cell or B-cell mitogens showed significant increases in blastic transformation of B-cells but nonsignificant effects on T-cells. Mice were inoculated with either of two types of antigens and exposed to the RFR, after which their spleens were assayed for antibody production. Antibody production to either antigen was reduced by RFR exposure, but only the difference for one of the antigens was statistically significant. Taken together, the results of this study show that thermogenic RFR levels (e.g., 14 W/kg) can have weak stimulatory effects on splenic B-lymphocytes but none on T-lymphocytes.

Sulek et al. (1980) found that the threshold for increases in CR^+ B-cells was about 5 W/kg for 30-minute exposures to 2.45-GHz RFR, yielding an energy-absorption threshold of 10 J/g. They noted that multiple exposures at levels below the threshold were cumulative if done within one hour of one another, but not if spaced 24 hours apart. However, Schlagel et al. (1980) presented results showing that RFR-induced increases in CR^+ B-cells depend on genetic factors. For example, CBA/J mice that have a specific histocompatibility haplotype showed marked increases in CR^+ cells due to RFR exposure, but mice having other haplotypes did not. Wiktor-Jedrzejczak et al. (1981) noted the findings of Schlagel et al. (1980) and suggested that the effect might be mediated by a humoral factor. As a test, they performed experiments involving implantation of spleen cells derived from RFR-exposed CBA/J mice into sham-exposed CBA/J mice and vice versa, and assayed both groups for circulating CR^+ spleen lymphocytes. For both donor and recipient mice exposed to RFR, the counts of circulating CR^+ spleen lymphocytes were higher than for their respective controls, thus supporting their hypothesis.

Smialowicz et al. (1981a) exposed CBA/J mice 10-12 weeks old to 2.45-GHz CW RFR at 15-40 mW/cm^2 (11-29 W/kg) for 30 minutes in an anechoic chamber. Six days later, assays of the percentages of CR^+ spleen cells and the numbers of nucleated spleen cells showed no significant differences in these two endpoints between sham-exposed mice and mice exposed at any of the RFR levels. Thus, these authors could not confirm the RFR-induced CR^+ increases found by Wiktor-Jedrzejczak and coworkers. Assuming that older mice may be more responsive, Smialowicz et al. (1981a) also exposed mice 14, 16, and 24 weeks old at 30 or 40 mW/cm^2. Only the 16-week-old mice exposed at 40 mW/cm^2 (29 W/kg) showed significantly higher percentages of CR^+ cells and smaller numbers of nucleated spleen cells.

Liburdy (1979) exposed mice for 15 minutes to 26-MHz RFR at 80 mW/cm^2, which produced core-temperature rises of 2-3 ^oC. The corresponding whole-body SAR was 5.6 W/kg. Other mice were heated in an oven at 63 ^oC for the same duration to obtain the same rises in core temperature. A decrease in the mean lymphocyte count (lymphopenia) and a rise in the mean neutrophil count (neutrophilia) were seen in the RFR-exposed mice, which persisted for 12 hours after exposure. The effects could be sustained and the recovery period prolonged by more RFR exposures at 3-hour intervals. By contrast, the oven-heated mice exhibited only slight effects. Those effects were absent for mice exposed to 26-MHz RFR at 50 mW/cm^2 or to 5-MHz RFR at 800 mW/cm^2, both of which yielded a whole-body SAR of about 0.4 W/kg (the basis for the 1982 ANSI standard).

Smialowicz et al. (1981b) exposed 16 rats almost continuously for 69-70 consecutive days to 970-MHz RFR at 2.5 W/kg. Blood samples taken from the rats after exposure showed no significant differences from sham-exposed rats in erythrocyte count, total or differential leukocyte counts, mean cell volume of erythrocytes, hemoglobin concentration, or hematocrit. Spleen cells cultured with various mitogens exhibited no significant differences in responses from sham-exposed rats. However, blood-serum analysis showed higher concentrations of triglyceride, albumin, and total protein for the RFR-exposed group, but those higher albumin and protein concentrations were within the normal ranges for the rat strain used and were not consonant with the absence of changes in erythrocyte assays, indicating that the rats may have been dehydrated. The authors noted that 2.5 W/kg is about half the basal metabolic rate of an adult rat, and they suggested that the triglyceride increases may have been due to thermal stress induced by RFR exposure. At 970 MHz, there probably were regions within the rat where local SARs were much higher than 2.5 W/kg, and such higher SARs could have affected the endocrinologic system of the rat.

Smialowicz et al. (1982a) exposed pregnant mice to 2.45-GHz RFR at 28 mW/cm^2 (16.5 W/kg) for 100 minutes daily. At 3 and 6 weeks of age, the pups were assessed for development of primary immune response to an antigen (SRBC), proliferation of lymphocytes *in vitro* by stimulation with mitogens, and *in vitro* activity of natural killer (NK) cells against lymphoma cells. No consistent significant differences were found between RFR-exposed and sham-exposed mice in any of the endpoints.

Smialowicz et al. (1982b) exposed mice to CW or pulsed 425-MHz RFR at SARs up to 8.6 W/kg. No differences were seen in mitogen-stimulated responses

of lymphocytes or in primary antibody response to sensitization with SRBC or another antigen (PVP) between RFR-exposed and sham-exposed mice, or between mice exposed to the CW or pulse-modulated RFR.

Smialowicz et al. (1983) exposed groups of mice for 1½ hours per day to 2.45-GHz RFR at several levels. For positive controls, other mice were injected with either hydrocortisone or saline. Splenic cells were then assayed *in vitro* for NK-cell activity by their cytotoxicity against mouse-lymphoma cells. Significant suppression of NK-cell activity was seen for 30 mW/cm^2 (21 W/kg), but such activity returned to normal within 24 hours after the last RFR exposure. However, this transient effect was not seen at 15 or 5 mW/cm^2 (10.5 or 3.5 W/kg). NK-cell activity was also assayed *in vivo*. Suppression of activity was seen in mice exposed at 30 mW/cm^2, but with return to normal several days after the last exposure. Hydrocortisone injection caused activity suppression both *in vitro* and *in vivo*.

Ortner et al. (1981) exposed rats to 2.45-GHz RFR for 8 hours at 2 or 10 mW/cm^2 (0.44 or 2.2 W/kg). Within 5 to 15 minutes after exposure, peritoneal mast cells were extracted, and histamine releases from the cells induced by a mitogen were determined. No significant differences from controls were seen in percentage of cell viability, percentage of cells, amount of histamine per cell, and cell diameter. For other rats similarly exposed, counts of total red and white cells were not affected by exposure at either RFR level, nor were blood-hemoglobin levels or percentages of lymphocytes and neutrophils relative to those for sham-exposed rats. The other types of cells were also unchanged by the RFR and serum biochemistry parameters were not affected by either RFR level.

Wong et al. (1985), seeking possible effects of prolonged exposure to low RFR levels in the HF band (3-30 MHz), conducted two experiments on rats. In the first experiment, 20 groups of 5 rats each were exposed to 20-MHz RFR at 1,920 mW/cm^2 (about 0.3 W/kg) for 6 hours per day, 5 days per week, and another 20 groups were sham-exposed as controls. After 8 days of treatment, 6 groups each of exposed and control rats were euthanized and examined for histopathology. This was also done for 7 groups each after 22 days and for the remaining 7 groups each after 39 days. In the second experiment, 12 rats were exposed to the RFR and 12 other rats were sham-exposed, but each rat was housed separately and all rats were euthanized after 6 weeks. On termination of the rats, blood samples were collected and the routine counts and blood-chemistry assays were done. The spleens were excised and weighed, and suspensions of spleen cells were prepared. Various other tissues were also examined for histopathology.

The first experiment yielded a significantly higher mean count of red blood cells and a significantly lower mean hemoglobin content for the rats terminated after 39 days of exposure than for the control group, but statistical analysis showed that those differences were not RFR-related. In the second experiment, however, no significant differences were seen in mean red blood cell count, hemoglobin, or any blood-chemistry parameters. Regarding histopathology, several abnormal conditions were found in rats of the first experiment, but those findings could not be attributed to the RFR exposure. All 24 rats in the second experiment were histologically normal at the end of the 6-week period of exposure.

In summary of the studies *in vivo* on the effects of chronic exposure on health, longevity, and resistance to disease, Prausnitz and Susskind (1962) exposed 100 mice to 9.3-GHz pulsed RFR at average power density of 100 mW/cm^2 (roughly 45 W/kg) for 4.5 minutes daily, which yielded a mean rise in body temperature of 3.3 ^oC, 5 days per week for 59 weeks. Controls were 100 sham-exposed mice. Some deaths occurred in both groups, which were attributed to a pneumonia infection introduced accidentally into the colony. However, the death rate was found to be lower in the RFR-exposed mice than in the sham-exposed mice, a finding ascribed to the protective effect of the daily rise in temperature ("fever") induced by the RFR. On necropsy, liver abscesses were found in some mice, but because of tissue breakdown (autolysis), the relative incidence in RFR-exposed and control mice could not be determined.

The authors reported that some mice had developed leukosis, which they described as a "cancer of the white blood cells," and that leukosis incidence was higher in the exposed mice than the control mice. The effect was real, but its interpretation by the authors was probably faulty. In dictionaries of medicine and pathology, leukosis is defined as an abnormal rise in the number of circulating white blood cells, and is not regarded as a form of cancer. Various factors can give rise to leukosis, including stress, disturbances of the endocrine system, and infection. The presence of pneumonia in the colony may have caused the observed liver abscesses.

Roberts and Michaelson (1983) reanalyzed the data of Prausnitz and Susskind (1962) with appropriate statistical treatment. They found that the results do not support a link between exposure to RFR and cancer development. They also remarked that the greater longevity of the RFR-exposed mice could be taken equally plausibly as indicating that the RFR was beneficial.

Szmigielski et al. (1980) injected mice with staphylococcal bacteria at a dose selected to yield a 60% survival rate on day 3 after injection. Before injection, the mice were sham-exposed or exposed to CW or pulsed 2.45-GHz RFR at 5 or 15 mW/cm^2 (2-3 or 6-9 W/kg) 2 hours per day for 6 or 12 weeks. For the mice exposed at 5 mW/cm^2 for 6 weeks, the survival rate was 80%; for those exposed at 5 mW/cm^2 for 12 weeks, it was 45%. The differences among those two RFR groups and the sham-exposed group were not statistically significant. The survival rates for the mice exposed at 15 mW/cm^2 for 6 or 12 weeks were 25% and 5%, respectively.

Liddle et al. (1987) sought effects of exposure to RFR at various ambient temperatures on the survival of mice given an LD_{50} dose of another strain of staphylococcus. They injected mice with that strain and exposed them to 2.45-GHz RFR at 10 mW/cm^2 (6.8 W/kg) for 5 days (4 hours per day) at 8 ambient temperatures in the range 19-40 ^oC and 50% relative humidity. For temperatures up to 31 ^oC, the percentages of RFR-exposed mice that survived the staphylococcus challenge were significantly higher than for sham-exposed mice. The results also indicated that most of the deaths were due to hyperthermia, and showed that exposure to RFR may be beneficial to infected animals at low and moderate ambient temperatures, in consonance with the findings of several other studies.

Guy and coworkers had exposed 100 rats to 2.45-GHz RFR at 0.5 mW/cm^2 and sham-exposed 100 other rats for 25 months in cylindrical waveguides under controlled-environmental and specific-pathogen-free conditions. Ten each of the two groups were euthanized after 13 months (the interim kill), as were 10 of the 12 RFR-exposed rats and 10 of the 11 sham-exposed rats that survived the 25-month regimen (the final kill).

Assays of suspensions of splenic cells at the interim kill showed significantly higher counts of T- and B-lymphocytes for the RFR-exposed rats than the sham-exposed rats, indicating that the RFR had stimulated the lymphoid system. However, there were no significant differences in T-cell and B-cell populations between the RFR and sham groups of the final kill, a possible indication of the onset of immunosenescence. The values of CR^+ for the RFR groups of both kills were lower than for the sham groups, but the differences were not significant, indicating no differences between RFR and sham groups in lymphocyte maturation. For both kills, there were no significant differences in percentages of plaque-forming cells in response to immunization with sheep red blood cells. Stimulation of splenic-cell suspensions with various mitogens yielded mixed results at the interim kill. No mitogen-stimulation results could be obtained for the terminal kill because the lymphocyte cultures failed to grow and respond to any of the mitogens.

Blood samples drawn periodically from all of the rats were assayed for various hematologic parameters and serum chemistry. By multivariate analyses, there were no overall significant differences between the RFR-exposed and sham-exposed rats in the hematologic parameters. Differences in thyroxine (T_4) levels between the RFR-exposed and sham-exposed rats were nonsignificant, indicating that the RFR had no effect on the hypothalamic-pituitary-thyroid feedback mechanism. As expected, however, the T_4 levels of both groups decreased significantly with age.

Toler et al. (1988) implanted cannulas in the aortas of 200 rats. After the rats recovered, 100 of them were concurrently exposed to 435-MHz pulsed RFR (1-μs pulses at 1,000 pps). Exposures were at 1 mW/cm^2 average power density for about 22 hours daily, 7 days a week, for 6 months. The whole-body SARs varied with time, ranging from 0.04 to 0.4 W/kg, with a mean of about 0.3 W/kg. The other 100 rats were concurrently sham-exposed. Blood samples were drawn cyclically without rat restraint or anesthesia and were assayed for the stress hormones ACTH, corticosterone, and prolactin in the plasma; plasma catecholamines; and hematologic parameters, including hematocrit and various blood cell counts. Also monitored were heart rates and arterial blood pressure. The results showed no significant RFR-induced differences between groups in any of the endpoints.

3.5.5 CONCLUSIONS

Overall, much of the early work seeking possible effects of RFR on suspensions of various classes of leukocytes exposed *in vitro* suffered from the lack of adequate control of cell temperature during exposure. In later studies in which effective control over culture temperature was exercised, nonsignificant differences were obtained with exposed cultures held at the same temperature as control cultures for the same durations. In studies where

culture-temperature elevation by RFR or conventional means did affect leukocytes adversely, the effects were clearly of thermal origin.

In early studies of RFR exposure of erythrocytes *in vitro*, hemolysis and potassium-ion (K^+) efflux were found for rabbit erythrocytes exposed at average power densities as low as 1 mW/cm^2. In subsequent investigations, however, the hemoglobin and K^+ losses from rabbit erythrocytes resulting from heating with RFR to 37 ^oC did not differ significantly from the losses obtained with conventional heating; the threshold SAR for effect was found to exceed 46 W/kg.

Studies seeking immunological effects of exposing animals to RFR *in vivo* yielded mixed results. Some investigators found that RFR exposure of mammals increased the proliferation of leukocytes or the production of antibodies (relative to controls), but with few exceptions, the measured or estimated SARs were well in excess of 1 W/kg. More subtle effects on mammalian immune systems were sought in more recent studies, making use of significant advances in assay methods and with attention to possible effects of non-RFR stress. Some of those investigations were directed toward the effects of RFR on the activity of natural killer (NK) cells, the results of which again showed that SARs much higher than 1 W/kg were necessary for effect.

More directly relevant to possible RFR effects on the human immune system would be studies in which animals are chronically exposed to RFR (preferably over virtually their entire lifetimes), to determine whether such exposure adversely affects their health, longevity, and resistance to natural disease or experimental challenge with various microorganisms or toxins therefrom. Some studies indicated that animals exposed to RFR for relatively short periods can withstand bacterial infection better than sham-exposed animals. Because of funding limitations, however, few studies involving chronic RFR exposure were carried out or repeated by other laboratories.

Probably the most comprehensive chronic investigation to date was the previously discussed University of Washington study, in which the authors exposed 100 rats to RFR and concurrently sham-exposed 100 other rats for essentially their full lifetimes (except those withdrawn for interim tests and those that expired before the end of the exposure regimen). Tests of 10 each RFR- and sham-exposed rats withdrawn after 13 months of treatment (interim kill) showed counts of splenic T- and B-lymphocytes that were significantly higher for the RFR than the sham group, an effect ascribed to stimulation of the lymphoid system by the RFR. However, this effect was absent in similar tests on completion of treatment, with the absence ascribed to immunosenescence. Longevity of the rats was not affected by the RFR at corresponding times during the exposure regimen.

No primary malignancies were found at the interim kill (in the rats younger than one year). Probably the most controversial finding of the entire study, however, was that among those older than one year, primary malignant lesions (of various kinds) were found in a total of 18 of the RFR-exposed rats but only 5 of the sham-exposed rats. The authors gave several cogent arguments to discount the biological significance of this finding. Among the arguments were that the difference between the RFR- and sham-exposed rats in

number of cases of each specific malignancy was nonsignificant and that because the numbers were so small, statistical significance could be attained only by combining them, an oncologically dubious procedure. Nevertheless, the issue has not yet been resolved.

The study of rats by Toler et al. (1988) is also noteworthy for the number of animals involved and the long exposure duration. As remarked by the authors, the absence of RFR-induced effects complement those of Guy and coworkers at the University of Washington.

3.6 PHYSIOLOGY AND BIOCHEMISTRY

The literature on physiological and biochemical effects associated with exposure to RFR is extensive. Many of the reported effects were associated with other events (e.g., changes in hormonal levels or stress adaptation), some are questionable for various reasons, and the medical significance of others is unclear.

3.6.1 METABOLISM AND THERMOREGULATION

Several studies have been done in which primates were exposed to RFR in the HF region (3-30 MHz). Bollinger (1971) exposed rhesus monkeys to 10.5-MHz or 19.3-MHz RFR for successive time intervals at successively higher power densities up to 600 mW/cm^2 (SAR about 0.2 and 0.6 W/kg, respectively), or to 26.6-MHz RFR at up to 300 mW/cm^2 (about 0.6 W/kg). Deep-body temperatures and EKGs were taken during exposure. No obvious indications of thermal stress, heart-rate increases, or other influences on the electrical events of the heart cycle due to the RFR were found.

The author also exposed rhesus monkeys to 10.5- or 26.6-MHz RFR for 1 hour at 200 or 105 mW/cm^2 (0.06 or 0.2 W/kg), or to 19.3-MHz RFR for 14 days (4 hours per day) at 115 mW/cm^2 (0.1 W/kg). Hematologic and blood-chemistry analyses were done before and after exposure. There were no significant differences between exposed and control monkeys for most of the cellular components of blood. Significant differences in mean counts of monocytes and eosinophils were seen, but were ascribed to conditions unrelated to RFR. The conclusions were similar for the blood-chemistry parameters. No abnormalities ascribable to exposure were seen in gross pathological and histopathological examinations.

In another study, Frazer et al. (1976) exposed rhesus monkeys to 26-MHz RFR at 500, 750, or 1,000 mW/cm^2 (1.0, 1.5, or 2.0 W/kg) for 6 hours, during which skin and rectal temperatures were measured. The results showed that the monkeys were in thermal equilibrium even at the highest RFR level; they were able to dissipate the additional heat from the RFR, and their thermoregulatory mechanisms were quite efficient in doing so. The authors noted that exposing a 3.6-kg monkey to 26-MHz RFR at 1,000 mW/cm^2 (2.0 W/kg) is equivalent to exposing a human 1.8 m (about 5 feet 11 inches) tall to the same frequency at 400 mW/cm^2.

In a third study, Krupp (1977) exposed rhesus monkeys for 3 hours to 15 or 20 MHz RFR at levels in the range 760-1,270 mW/cm^2 (0.6-1.3 W/kg). Again, the results showed that the additional heat from the RFR was readily

accommodated by their thermoregulatory mechanisms. Exposure to 20-MHz RFR at 1,270 mW/cm^2 was calculated to be equivalent to human exposure to 20-MHz at 225 mW/cm^2.

Last, Krupp (1978) did a followup study on 18 rhesus monkeys that had been exposed 1-2 years previously to 15-, 20-, or 26-MHz RFR for up to 6 hours at least twice at levels in the range 500-1270 mW/cm^2. No RFR-related variations from normal values of hematologic and biochemical blood indices or of physical conditions were found.

Ho and Edwards (1979) used oxygen-consumption rate as an indicator of stress in mice. Mice were exposed to 2.45-GHz RFR in a waveguide system that permitted continuous monitoring of SAR during exposure. The exposures were for 30 minutes, during which oxygen-consumption rates and SARs were determined at 5-minute intervals. The oxygen-consumption rates were converted into specific metabolic rates (SMRs) and expressed in the same units as the SARs (W/kg). Oxygen-consumption rates were also measured at 5-minute intervals for 30 minutes before and after exposure.

At the highest input power, the mean SAR decreased from 56 to 39 W/kg during 30 minutes of exposure, and the mean SMR decreased from 17.5 to 14 W/kg, thereby decreasing the total thermal burden from 74 to 54 W/kg. Apparently the mice sought to diminish their thermal burdens by altering their body configurations during exposure to minimize the RFR-absorption rates; they also reduced their oxygen consumption. Smaller changes were seen at SARs of 23.6 W/kg and 10.4 W/kg, and insignificant changes at 5.5 and 1.6 W/kg. The SMR decreases for SARs of 10.4 W/kg and higher were ascribed to thermal stress, and the onset level was about the same as the basal metabolic rate of the mouse (9 W/kg). After exposure completion, oxygen consumption rates returned to normal.

To study voluntary thermoregulation in the rat, Stern et al. (1979) trained fur-clipped rats in a cold chamber to press a lever that turned on an infrared lamp. When the rats were exposed to 2.45-GHz RFR for 15-minute periods, the rate at which they turned on the lamp decreased as a function of the RFR level, which ranged from 5 to 20 mW/cm^2 (1-4 W/kg). The rats responded to maintain a nearly constant thermal state. In the absence of the RFR, the lamp was the sole heat source. With the RFR present, the rats compensated by reducing their response rate, thereby lowering the IR heat contribution. Thus, voluntary thermoregulation is an indicator of the additional thermal burden of RFR.

Adair and Adams (1980) trained three squirrel monkeys to regulate their environmental temperature (T_a) behaviorally by adjusting the flows of air at various temperatures into an exposure chamber. The monkeys were then exposed to 2.45-GHz RFR for 10-minute periods at levels in the range 1-22 mW/cm^2 (0.15-3.3 W/kg). They were also sham-RFR-exposed and exposed to infrared radiation (IR) of equivalent power densities. At an RFR level of about 7 mW/cm^2 and higher, all were stimulated to select a lower T_a. This RFR level represents a whole-body-SAR threshold of 1.1 W/kg or 20% of the resting metabolic rate of the squirrel monkey. The thermoregulatory behavior was highly efficient, and the skin and rectal temperatures remained stable, even

at 22 mW/cm^2 (3.3 W/kg), where the preferred T_a was lower by up to 4 ^{o}C. Comparable reductions in the T_a selected did not occur for exposure to the IR.

Bruce-Wolfe and Adair (1985) investigated the ability of squirrel monkeys to vary the level of 2.45-GHz RFR as a source of thermalizing energy. First, they trained four monkeys to regulate the temperature of the air in the exposure chamber, T_a, by selecting air streams at 10 and 50 ^{o}C successively, i.e., temperatures below and above the thermoneutral level (about 30 ^{o}C). The resulting mean T_a was about 35 ^{o}C.

After stable performance was achieved, the 50-^{o}C air source was replaced with 2.45-GHz RFR at 20 mW/cm^2 (3 W/kg) and thermoneutral 30-^{o}C air. Thus, only that RFR and air source were activated whenever the monkeys demanded heat, and only the 10-^{o}C air source was activated when cooling was demanded. Sessions with RFR at 25 and 30 mW/cm^2 (3.75 or 4.5 W/kg) were also conducted. The results indicated that the monkeys were readily able to use the thermal energy from the RFR for thermoregulation instead of the 50-^{o}C air source, and were thereby able to maintain normal rectal temperature.

Adair et al. (1985) examined the effects of long-term RFR exposure on behavioral and physiological thermoregulation in the squirrel monkey. The exposures were for 15 weeks, 40 hours/week, to 2.45-GHz CW RFR at 1 or 5 mW/cm^2 (0.16 or 0.8 W/kg) at environmental temperatures of 25, 30, or 35 ^{o}C. Fourteen monkeys were trained to select a preferred T_a, and were treated concurrently in fours, one pair each for RFR- and sham-exposure. The pairs used for sham-exposure in a given experiment were RFR exposed in the next experiment, with 2-3 months between experiments for the dissipation of any residual effects.

Physiologic changes related to thermoregulation were determined periodically before, during, and after such treatment, including body mass, blood properties, skin temperatures, oxygen consumption, colonic temperature, and foot sweating. Each monkey was also trained to select its preferred environmental temperature T_a as in the study above, and their corresponding colonic temperatures and mean skin temperatures were measured.

The results for environmental temperature 25 ^{o}C or 30 ^{o}C showed no change in preferred T_a during exposure at 1 mW/cm^2 (0.16 W/kg). At 35 ^{o}C and 1 mW/cm^2 or at all three environmental temperatures and 5 mW/cm^2 (0.8 W/kg), however, the monkeys selected cooler environments (T_as 1 to 3 ^{o}C lower). Sweating was higher at 35 ^{o}C, but was not enhanced by exposure to the RFR at either level. Colonic temperature was not affected, but skin temperature varied with environmental temperature and RFR exposure in an unreliable way.

Mean body mass during sham-exposure, with proper consideration of seasonal variations, increased reliably at 25 ^{o}C, increased slightly at 30 ^{o}C, and decreased slightly at 35 ^{o}C. Reliable decreases in body mass at all three temperatures were found for exposure at 5 mW/cm^2 (0.8 W/kg). However, the authors could not ascribe those decreases to reductions in food intake, because precise measurements of the food and water intake by the monkeys were not possible. No significant changes in blood indices or in other physiological characteristics due to the RFR were found.

Lotz and Saxton (1987) studied the vasomotor and metabolic responses of five rhesus monkeys exposed to 225-MHz CW RFR with body axis parallel to the electric component (E-orientation). Two protocols were used. The first protocol was designed to determine the threshold for the onset of vasomotor responses: After the monkeys equilibrated for 120 minutes, each was given repetitive 10-minute exposures at successively higher power densities until a marked vasomotor response was evidenced by a rapid change in the temperature of the tail skin. After each 10-minute exposure, the monkey was allowed to reequilibrate to within 0.3 ^{o}C of its pre-exposure value.

RFR levels in the range 1.2-12.5 mW/cm^2 (0.3-3.6 W/kg) were used. The time interval needed for reequilibration varied from about 10 to 60 minutes, depending on the RFR level. Each monkey was used in four such experiments, two each at 20 and 26 ^{o}C.

Results for the first protocol showed that metabolic response occurred before tail vasodilation was manifested (i.e., at a lower RFR level). At 20 ^{o}C, metabolic heat production was not altered at 1.2 mW/cm^2 (0.3 W/kg) but declined with increasing RFR level. At 26 ^{o}C, the rate of metabolic heat production before exposure was 28% below that at 20 ^{o}C, and was not altered by the 10-minute exposures. Analysis of the data indicated that the lowest RFR level that reliably altered metabolic heat production during such 10-minute exposures was in the range 5-7.5 mW/cm^2 (1.4-2.1 W/kg).

In the second protocol, thermoregulatory adjustments in the steady state during exposure were evaluated. The monkeys were equilibrated for 120 minutes at 20 ^{o}C and then given single 120-minute exposures at levels in the range 0-10 mW/cm^2 (0-2.9 W/kg). Data were collected for 10-60 minutes after exposure. The monkeys were also similarly treated at 26 ^{o}C, but at levels in the range 0-7.5 mW/cm^2 (0-2.1 W/kg).

During the last 30 minutes of pre-exposure, the mean metabolic heat production was 2.26 W/kg at 26 ^{o}C and 3.13 W/kg at 20 ^{o}C; it declined sharply during RFR exposure at 20 ^{o}C and remained essentially unchanged during RFR exposure at 26 ^{o}C. Also evident was progressive recruitment of metabolic and vasomotor responses at 20 ^{o}C. At both ambient temperatures, the mean colonic temperature during the last 30 minutes of RFR exposure was higher than for the last 30 minutes of sham-exposure, even at 2.5 mW/cm^2 (0.7 W/kg), which was below threshold for thermoregulatory effector action. This result indicated that the thermoregulatory responses could not fully compensate for the heat generated by the RFR in the cooler environment.

3.6.1.1 SUMMARY

Bollinger (1971) exposed rhesus monkeys to 10.5-MHz or 19.3-MHz RFR at successively higher power densities up to 600 mW/cm^2 (about 0.2 or 0.6 W/kg, respectively), or to 26.6-MHz RFR at up to 300 mW/cm^2 (0.6 W/kg). Colonic body temperatures and EKGs taken during exposure indicated no obvious indications of thermal stress, heart-rate increases, or other influences on the electrical events of the heart cycle due to the RFR. Also, rhesus monkeys were exposed to 10.5- or 26.6-MHz RFR for 1 hour at 200 or 105 mW/cm^2 (0.06 or 0.2 W/kg), or to 19.3-MHz RFR for 14 days (4 hours per day) at 115 mW/cm^2 (0.1 W/kg). Hematologic and blood-chemistry analyses done before and after

exposure showed no significant differences between exposed and control monkeys for most of the cellular components of blood. Significant differences in mean counts of monocytes and eosinophils unrelated to RFR were seen. No abnormalities ascribable to exposure were seen in gross pathological and histopathological examinations.

Frazer et al. (1976) exposed rhesus monkeys to 26-MHz RFR at levels up to 1,000 mW/cm^2 (2.0 W/kg) for 6 hours, during which skin and rectal temperatures were measured. The monkeys remained in thermal equilibrium even at the highest RFR level, and their thermoregulatory mechanisms were able to dissipate the additional heat from the RFR efficiently. Krupp (1977) exposed rhesus monkeys for 3 hours to 15 or 20 MHz RFR at levels up to 1,270 mW/cm^2 (1.3 W/kg). Again, the thermoregulatory mechanisms of the monkeys readily accommodated the additional heat. Krupp (1978) followed up on 18 rhesus monkeys that had been exposed 1-2 years previously to 15-, 20- or 26-MHz RFR for up to 6 hours at least twice at levels in the range 500-1270 mW/cm^2. No RFR-related variations from normal values of hematologic and biochemical blood indices or of physical conditions were found.

Ho and Edwards (1979) exposed mice for 30 minutes to 2.45-GHz RFR in a waveguide system that permitted measurement of oxygen-consumption rates and SAR during exposure. Such measurements were done at 5-minute intervals during exposure. Oxygen-consumption rates were also measured at 5-minute intervals for 30 minutes before and after exposure. The oxygen-consumption rates were converted into specific metabolic rates (SMRs) and expressed in the same units as the SARs (W/kg). At the highest RFR level, both the mean SAR and mean SMR had steadily decreased during exposure, thereby decreasing the total thermal burden of the mice. Apparently, they sought to diminish their thermal burdens by altering their body configurations during exposure to minimize the RFR-absorption rates, and reduced their oxygen consumption. After exposure completion, oxygen consumption rates returned to normal.

To study voluntary thermoregulation in the rat, Stern et al. (1979) trained fur-clipped rats in a cold chamber to press a lever that turned on an infrared lamp. The rats were then exposed to 2.45-GHz RFR for 15-minute periods at increasing levels, ranging from 5 to 20 mW/cm^2 (1-4 W/kg). As the RFR level was raised, the rats responded to maintain a nearly constant thermal state by decreasing the rate at which they turned on the lamp.

Adair and Adams (1980) trained three squirrel monkeys to regulate their environmental temperature (T_a) behaviorally by adjusting the flows of air at various temperatures into an exposure chamber. The monkeys were then exposed to 2.45-GHz RFR for 10-minute periods at levels in the range 1-22 mW/cm^2 (0.15-3.3 W/kg). They were also exposed to infrared radiation (IR) of equivalent power densities while being sham-exposed to RFR. For the RFR at about 7 mW/cm^2 (1.05 W/kg) and higher, all were stimulated to select a lower T_a, indicating the existence of a threshold of 1.1 W/kg whole-body SAR or 20% of the resting metabolic rate of the squirrel monkey. Comparable reductions in selected T_a did not occur for exposure to the IR.

Bruce-Wolfe and Adair (1985) investigated the ability of squirrel monkeys to vary the level of 2.45-GHz RFR as a thermal energy source. They trained four monkeys to successively select air streams having temperatures 20

^{o}C below and above 30 ^{o}C, the thermoneutral temperature in the exposure chamber. The resulting mean T_a was about 35 ^{o}C. Then the 50-^{o}C air source was replaced with 2.45-GHz RFR at 20 mW/cm^2 (3 W/kg) and 30-^{o}C air. Thus, only the latter two sources were activated whenever the monkeys demanded heat, and only the 10-^{o}C air source was activated whenever they demanded cooling. The results indicated that the monkeys were readily able to use the thermal energy from the RFR for thermoregulation instead of the 50-^{o}C air source, and were thereby able to maintain normal rectal temperature.

Adair et al. (1985) performed similar experiments to determine the effects of long-term RFR exposure on thermoregulation. The exposures were for 15 weeks, 40 hours/week, to 2.45-GHz CW RFR at 1 or 5 mW/cm^2 (0.16 or 0.8 W/kg) at T_as of 25, 30, or 35 ^{o}C. Fourteen monkeys were trained to select a preferred T_a, and were treated concurrently in fours, one pair each for RFR- and sham-exposure. The pairs used for sham-exposure in a given experiment were exposed to RFR in the next experiment, with 2-3 months between experiments for dissipation of any residual effects. The results for 25 ^{o}C or 30 ^{o}C showed no changes in the preferred T_a during exposure at 1 mW/cm^2. However, at 35 ^{o}C and 1 mW/cm^2 (0.16 W/kg) or at all three T_as and 5 mW/cm^2 (0.8 W/kg), the monkeys selected cooler environments (T_as 1 to 3 ^{o}C lower). Colonic temperatures were not affected, but skin temperatures varied with T_a and RFR exposure in an unreliable way.

Lotz and Saxton (1987) studied the vasomotor and metabolic responses of five rhesus monkeys exposed to 225-MHz CW RFR with body axis parallel to the electric component. In the first of two protocols, each monkey was given 10-minute RFR exposures at successively higher levels, with enough time after each exposure for the monkey to return to its pre-exposure equilibrium, until a marked vasomotor response was evidenced by a rapid change in tail-skin temperature. RFR levels in the range 1.2-12.5 mW/cm^2 (0.3-3.6 W/kg) were used. Each monkey was used in four such experiments, two each at 20 and 26 ^{o}C. At 20 ^{o}C, metabolic heat production was not altered at 1.2 mW/cm^2 (0.3 W/kg) but declined with increasing RFR level. At 26 ^{o}C, the rate of metabolic heat production before exposure was well below that at 20 ^{o}C, and was not altered by the 10-minute RFR exposures. The lowest RFR level that reliably altered metabolic heat production during such 10-minute exposures was in the range 5-7.5 mW/cm^2 (1.4-2.1 W/kg).

In the second protocol, the monkeys were equilibrated at 20 ^{o}C and then given single 120-minute exposures at levels in the range 0-10 mW/cm^2 (0-2.9 W/kg). The monkeys were also similarly treated at 26 ^{o}C, but at RFR levels up to 7.5 mW/cm^2 (2.1 W/kg). Mean metabolic heat production dropped sharply during RFR exposure at 20 ^{o}C, but remained essentially unchanged during RFR exposure at 26 ^{o}C. Also evident was progressive recruitment of metabolic and vasomotor responses at 20 ^{o}C. At both ambient temperatures, the mean colonic temperature during the last 30 minutes of RFR exposure was higher than for the last 30 minutes of sham-exposure, even at 2.5 mW/cm^2 (0.7 W/kg), which was below the threshold for thermoregulatory effector action. This result indicated that thermoregulatory responses could not fully compensate for the heat generated by the RFR even in the cooler (20-^{o}C) environment.

In overall summary, the thermal basis for various effects of RFR on the autonomic thermoregulatory systems of mammals and on their behavioral

thermoregulatory responses to RFR is evident. Especially noteworthy are the results for primates because of their far greater similarities to humans than the other animals studied.

3.6.2 ENDOCRINOLOGY

Exposure of mammals to RFR has yielded rather inconsistent effects on the endocrine system. In general, effects are apparently related to either the heat load associated with RFR or the stress induced by RFR, and possibly by other circumstances.

Cairnie et al. (1980) sham-exposed or exposed unanesthetized mice for 16 hours to 2.45-GHz RFR at 50 mW/cm^2 (60 W/kg), after which they were euthanized. Rectal and testis temperatures versus time after exposure cessation were measured, and the resulting cooling curves were used to determine the temperatures at exposure end. The mean rectal temperature for the RFR group was significantly higher than for the sham group, but the mean testis temperatures of the RFR and sham groups did not significantly differ, indicating that the thermoregulatory system of the testes was able to compensate fully for the increased thermal burden from RFR at close to lethal level.

Experiments were also performed in which arrays of conscious mice were exposed for various durations to 2.45-GHz RFR at levels in the range 21-37 mW/cm^2, after which testicular cells were examined for damage, and abnormal sperm were counted. The corresponding ranges of whole-body and testicular SARs were 25.3-44.5 W/kg and 8.4-14.8 W/kg, respectively. The results showed no significant differences between the RFR-exposed and sham-exposed mice in mean percentages of damaged testicular cells, sperm counts, or percentages of abnormal sperm.

Lebovitz and Johnson (1983) sham-exposed or exposed unanesthetized male rats to 1.3-GHz RFR for 9 days (6 hours per day) during a 2-week period. The whole-body SAR was 6.3 W/kg, which produced a mean rise in core temperature of 1.5 ^{o}C. After treatment completion, groups of rats were weighed and decapitated at intervals corresponding to ½, 1, 2, and 4 cycles of spermatogenesis. Spermatids resistant to homogenization were counted in the right testis, and daily sperm production was calculated. The left testis was processed for examination by light microscopy.

RFR-exposed rats yielded 87.6% normal sperm after a half-cycle of spermatogenesis versus 95.8% for sham-exposed rats. The difference was significant, but most of the abnormal sperm in the RFR group were from one rat with 45.5% abnormal sperm, which rendered the finding suspect. There was no significant difference in the weight of seminal vesicles between RFR-exposed and sham-exposed rats, indicating that exposure at 6.3 W/kg was not deleterious to testosterone production. This finding was supported by histological evaluations by light microscopy.

Lebovitz and Johnson (1987) subsequently exposed 16 male rats once for 8 hours unrestrained in individual cylindrical waveguides to 1.3-GHz CW RFR at 9 W/kg, a level selected to yield a core-temperature rise of 4.5 ^{o}C and stated to be lethal for chronic exposure. Sixteen other rats were sham-exposed.

Subgroups at ½, 1, 2, and 4 cycles of spermatogenesis following treatment were analyzed for testis mass and daily sperm production as in the previous study. Also, trunk blood was assayed for follicle-stimulating hormone and leutinizing hormone.

There were no significant differences between RFR-exposed and sham-exposed rats in any of the endpoints, except for a decline in epididymal sperm count 26 days (2 cycles of spermatogenesis) after RFR exposure. However, the authors remarked that in view of the negative results in the many other endpoints examined, the single positive result is highly questionable. They also noted that a differential sensitivity of germ cells at this stage of maturation had been reported for conventional heating of the testes.

In the first of several studies, Lotz and Michaelson (1978) first "gentled" rats for 2 weeks before exposure by weighing and handling them at least four times a week, and behaviorally equilibrating each rat by taking its colonic temperature and putting it into an exposure cage for 3-5 hours for several days before use. Adrenal-axis activity during equilibration was determined by placing groups of rats in the exposure chamber for 30, 60, 90, 120, 150, or 180 minutes, measuring colonic temperature before and after each interval, and assaying the blood for corticosterone (CS) level. The results showed a rapid rise of colonic temperature and CS level during the first 30 minutes to an approximate plateau, followed by a return to baseline values by the end of 180 minutes, thus demonstrating the need for such equilibration prior to exposure.

The authors then exposed groups of unanesthetized gentled rats to 2.45-GHz RFR for 30, 60, or 120 minutes at levels up to 60 mW/cm^2 (9.6 W/kg), and measured colonic temperatures and CS levels after exposure. A plot of mean postexposure colonic temperature versus exposure duration showed a small but significant rise after 30 minutes at 13 mW/cm^2 (2.1 W/kg); exposures for 30 minutes at higher levels yielded mean temperature rises approximately proportional to RFR level. The mean CS level rose nonsignificantly for durations up to 120 minutes at 13 mW/cm^2 (2.1 W/kg), up to 60 minutes at 20 mW/cm^2 (3.2 W/kg), and 30 minutes at 30 mW/cm^2 (4.8 W/kg). All other CS rises were significant and highly correlated with rises in colonic temperature. The estimated threshold values for adrenal-axis stimulation were 30-50 mW/cm^2 (4.8-8.0 W/kg) for 60-minute exposures and 15-20 (2.4-3.2 W/kg) mW/cm^2 for 120-minute exposures. The latter range is somewhat less than half the rat's resting metabolic rate.

Lu et al. (1985), noting inconsistencies in the findings of various investigators, described their studies with male Long-Evans rats from two suppliers, Blue-Spruce (BS) and Charles River (CR). Prior to treatment, the rats were acclimated and gentled, which included observation for 4 to 11 days, 2 weeks of handling, and 3 to 5 days of simulated exposure.

Treatment consisted of concurrently exposing groups of 4 rats each in individual cages from above to 2.45-GHz RFR (or sham-exposure) in an anechoic chamber. The minimum separation between rats was 18 cm. The normalized SAR was 0.19 W/kg per mW/cm^2. The seven protocols below were used, with each group of rats equilibrated for 3 hours before the start of treatment. The

rats were decapitated right after treatment end and their blood was assayed for serum T_4 concentration.

(A) Single exposures of one group each of BS rats only, for 1 hour at 0 (sham), 1, 5, 10, 20, 40, 50, 60, or 70 mW/cm^2.

(B) Single 2-hour exposures of BS rats at 0, 5, 10, or 20 mW/cm^2, and of CR rats at 25, 30, or 40 mW/cm^2.

(C) Single 4-hour exposures of BS rats at 0, 1, 5, 10, or 20 mW/cm^2, and of CR rats at 0, 0.1, 1, 10, 25, or 40 mW/cm^2.

(D) Single 8-hour exposures of BS rats only, at 0, 1, 5, 10, or 20 mW/cm^2.

(E) Single 4-hour exposures of CR rats only, at 0, 0.1, 1, 10, 25, or 40 mW/cm^2, followed by sham-exposure for 7 hours starting 17 hours after RFR exposure, with endpoints measureed at the end of sham-exposure (24 hours after RFR-exposure completion).

(F) Three consecutive daily 4-hour exposures of CR rats only, at 0, 1, 10, 20, 30, 40, or 55 mW/cm^2.

(G) Ten consecutive daily 4-hour exposures of CR rats only, 5 days a week, for 2 weeks at 1, 10, 20, 25, 30, or 40 mW/cm^2.

Results for the 1-hour exposures showed no apparent dose dependence: Significantly higher T_4 levels were obtained for rats exposed at 40 or 70 mW/cm^2, but not at 50 or 60 mW/cm^2 or at 20 mW/cm^2 or lower. For the 2-hour exposures, the T_4 levels for both BS and CR rats were higher at 25, 30, or 40 mW/cm^2 but not significantly affected at 20 mW/cm^2 or lower. However, the authors found that the normal T_4 concentrations for CR rats were higher than for BS rats, so those and later results were reevaluated by separately comparing T_4 levels for the RFR-exposed rats from each supplier with sham-exposed rats from the same supplier. When that was done for the 2-hour exposures, there were no significant RFR-induced changes in concentration of T_4.

For the 4-hour exposures, only results for BS rats were displayed. Their T_4 levels, compared to those for sham-exposure, were significantly higher at 1 mW/cm^2, not significantly changed at 5 or 10 mW/cm^2, and were significantly lower at 20 mW/cm^2. For the remaining protocols, there were no significant RFR-induced T_4 alterations except for the CR rats given the three consecutive daily 4-hour exposures at 40 mW/cm^2, for which the T_4 level was significantly lower than for shams.

Because of their protocol design, the authors believed that they had avoided nonspecific reactions to stressful stimuli, but not those from repeated sham-exposures. However, they remarked: "From the viewpoint of environmental health, changes in serum thyroxine cannot be used as an indicator of a past history of microwave exposure due to its limited magnitude of response and its sensitivity to extraneous factors."

Lu et al. (1986) sought to determine the influence of confounding factors in studies of effects of RFR on the adrenal cortex. Serum CS concentration was used as the index of adrenocortical function. After acclimation and gentling, groups of rats were subjected to 10 protocols involving single or multiple 2-hour or 4-hour exposures to 2.45-GHz RFR at levels in the range 0.1-55 mW/cm^2 (0.02-11 W/kg) and sham-exposures. Their protocols included:

(1) CS concentrations in urine and its excretion rates, measurements of colonic temperature, and inhalation of ether to determine the responsiveness of the hypothalamic-hypophysial-adrenocortical axis to an intensive stimulant.

(2) Injection of ethanol to lower the preexposure body temperature and to limit the heat-dissipation ability of the rat.

(3) Hair removal to increase heat dissipation during RFR exposure.

Rises in colonic temperature and CS concentration were found to be dependent on RFR level with distinct thresholds, but showed acclimation (diminution of effect with repetition). For repetitive 4-hour exposures, the threshold for colonic-temperature rise was 10 mW/cm^2 (2 W/kg) at the first exposure, 30 mW/cm^2 (6 W/kg) at the third exposure, and 25 mW/cm^2 (5 W/kg) at the tenth exposure. The thresholds for change of CS concentration was 40 mW/cm^2 (8 W/kg) at the first exposure and 55 mW/cm^2 (11 W/kg) at the third exposure, but the rats exposed 10 times at levels up to 40 mW/cm^2 (8 W/kg) showed no changes. The changes observed were no longer present 24 hours after exposure. For the sham-exposures, baseline colonic temperature was higher after the tenth than the first treatment, but CS concentration did not change.

Injection of ethanol lowered the baseline colonic temperature and raised the CS concentration, effects not observed for saline-injected controls. Exposures for 2 hours at 1 or 10 mW/cm^2 following ethanol injection yielded lower colonic temperatures than for similar exposures after saline injection, but were higher for ethanol-injected rats exposed at 40 or 50 mW/cm^2. Interaction of ethanol and RFR at 10 and 20 mW/cm^2 also yielded higher CS concentrations than in saline-injected rats. A single exposure at 50 mW/cm^2 was lethal in two rats given ethanol.

Hair removal did not affect the baseline colonic temperatures and CS concentrations significantly, but it decreased RFR-induced hyperthermia and CS stimulation.

The authors concluded that the adrenal response of the rat to RFR is quantifiable with respect to RFR level or colonic temperature, with no response to RFR in the absence of a rise in colonic temperature. They indicated that adrenal stimulation minimally required an RFR level of 20 mW/cm^2 (4 W/kg) or a 0.7-^{o}C increase in colonic temperature. They also remarked that RFR at less than 4 W/kg in ambient temperatures well above 24 ^{o}C may induce hyperthermic stimulation of adrenal secretion.

Lotz and Podgorski (1982) implanted a catheter in the jugular vein of 6 rhesus monkeys for monitoring levels of cortisol, thyroxine (T_4), and growth

hormone (GH). They collected blood samples from each monkey hourly for 24 hours and measured colonic temperature with an indwelling probe. At the same clock time during the 24-hour period, each monkey was exposed for 8 hours to 1.29-GHz RFR at 20, 28, or 38 mW/cm^2 (2.1, 3.0, or 4.1 W/kg). The authors noted that the resting metabolic rate (RMR) of a rhesus monkey is 2.4 W/kg. Three sessions at each level were alternated with sessions of sham-exposure at intervals of 10-14 days for recovery.

Hematocrit and hemoglobin, monitored before and after each session, showed no significant decline. Samples of blood plasma were assayed for cortisol, T_4, and GH. The data collected for the same clock periods of the three sessions at each RFR level were averaged, to yield a 24-hour temporal series of mean values for each condition.

For the sham-exposure sessions, the mean rectal temperature showed a slight 24-hour periodicity, with minimum values during the times when the chamber lights were off. It rose within 2 hours after the beginning of RFR exposure to plateaus that were dependent on RFR level, but returned to the control profile within 2 hours after exposure end.

For sessions at 20 and 28 mW/cm^2, the mean plasma-cortisol levels did not differ significantly from those for sham-exposure sessions, but rose significantly above control level during sessions at 38 mW/cm^2. The levels then diminished to control values, indicating that the effect was transient. The authors suggested: the existence of a threshold between 28 and 38 mW/cm^2 (3.0 and 4.1 W/kg), that the rises in plasma-cortisol levels were associated with rectal-temperature elevations of about 1.7 ^{o}C, and that the results support the hypothesis that adrenocortical effects of RFR are thermally induced. For all RFR levels, no significant differences in mean GH or T_4 levels were seen at corresponding times during RFR and sham sessions.

3.6.2.1 SUMMARY

Cairnie et al. (1980) exposed unanesthetized male mice for 16 hours to 2.45-GHz RFR at 50 mW/cm^2 (60 W/kg) and determined their rectal and testis temperatures at exposure end. The mean rectal temperature was significantly higher than for sham-exposed mice, but the mean testis temperature did not differ significantly, showing that the thermoregulatory system of the testes was able to compensate fully for the increased thermal burden from RFR at close to lethal level. Also, conscious mice exposed for various durations to 2.45-GHz RFR in the range 21-37 mW/cm^2 exhibited no testicular cell damage or abnormal sperm counts. The corresponding ranges of whole-body and testicular SARs were 25.3-44.5 W/kg and 8.4-14.8 W/kg.

Lebovitz and Johnson (1983) exposed unanesthetized male rats to 1.3-GHz RFR for 9 days (6 hours per day) at a whole-body SAR of 6.3 W/kg, which produced a mean core-temperature rise of 1.5 ^{o}C. On exposure completion, groups of rats were weighed and euthanized at intervals corresponding to ½, 1, 2, and 4 cycles of spermatogenesis. RFR-exposed rats yielded 87.6% normal sperm after a half-cycle of spermatogenesis versus 95.8% for sham-exposed rats. The difference was significant, but most of the abnormal sperm in the RFR group were from one rat with 45.5% abnormal sperm, which rendered the finding suspect. There was no significant difference in the mean weight of

seminal vesicles, indicating that exposure at 6.3 W/kg was not deleterious to testosterone production. This finding was supported by histological evaluations by light microscopy.

Lebovitz and Johnson (1987) exposed unrestrained male rats for 8 hours to 1.3-GHz CW RFR at 9 W/kg, selected to yield a core-temperature rise of 4.5 ^{o}C and stated to be lethal for chronic exposure. Subgroups at ½, 1, 2, and 4 spermatogenesis cycles following exposure were analyzed for testis mass and daily sperm production as in the previous study. Trunk blood was assayed for follicle-stimulating hormone and leutinizing hormone. There were no significant differences between RFR-exposed and sham-exposed rats in any of the endpoints, except for a decline in sperm count 2 cycles of spermatogenesis after RFR exposure. However, the authors remarked that a single positive result among the negative results for all of the many other endpoints studied is highly questionable. They also noted that a differential sensitivity of germ cells at this stage of maturation had been reported for conventional heating of the testes.

Lotz and Michaelson (1978) first "gentled" rats for 2 weeks before RFR exposure by weighing and handling them at least four times a week, and behaviorally equilibrating each rat by taking its colonic temperature and putting it into an exposure cage for 3-5 hours for several days before use. They had observed a rapid rise in colonic temperature and corticosterone (CS) levels in the blood of the rat in the first 30 minutes of occupancy in the exposure chamber, followed by return to baseline values by the end of 180 minutes, thus proving the need for such equilibration before exposure.

The authors then exposed unanesthetized gentled rats to 2.45-GHz RFR at up to 60 mW/cm^2 (9.6 W/kg) for up to 120 minutes and measured colonic temperatures and CS levels after exposure. The mean colonic temperature showed a small but significant rise after 30 minutes at 13 mW/cm^2 (2.1 W/kg), with 30-minute exposures at higher levels yielding mean temperature rises approximately proportional to RFR level. The mean CS level increased nonsignificantly for durations up to 120 minutes at 13 mW/cm^2 (2.1 W/kg), up to 60 minutes at 20 mW/cm^2 (3.2 W/kg), and 30 minutes at 30 mW/cm^2 (4.8 W/kg). The results yielded threshold values for adrenal-axis stimulation of 30-50 mW/cm^2 (4.8-8.0 W/kg) for 60-minute exposures and 15-20 (2.4-3.2 W/kg) mW/cm^2 for 120-minute exposures. The latter range is somewhat less than half the resting metabolic rate of the rat.

Lu et al. (1985) studied the effects of 2.45-GHz RFR on serum T_4 concentration in male Long-Evans rats from two suppliers, Blue-Spruce (BS) and Charles River (CR). The normalized SAR was 0.19 W/kg per mW/cm^2. The rats were acclimated and gentled before exposure. Seven protocols were used, involving exposures at various RFR levels up to 70 mW/cm^2 for up to 8 hours. At treatment end, the rats were euthanized and assayed for serum T_4 concentration.

Results for 1-hour exposures at up to 70 mW/cm^2 showed no dependence of T_4 concentration on RFR level. For 2-hour exposures, the T_4 levels for both BS and CR rats were significantly higher at 25, 30, or 40 mW/cm^2 than for sham-exposed rats, but were not significantly affected at 20 mW/cm^2 or lower. However, the normal T_4 concentrations for CR rats were higher than for BS

rats, so those and subsequent results were reevaluated by separately comparing T_4 levels for the RFR-exposed rats from each supplier with sham-exposed rats from the same supplier. With that change, no significant RFR-induced changes in T_4 concentration were seen for the 2-hour exposures.

For 4-hour exposures, only the results for BS rats exposed at up to 20 mW/cm^2 were shown. Their T_4 levels, compared to those for sham-exposure, were significantly higher at 1 mW/cm^2, not significantly changed at 5 or 10 mW/cm^2, and were significantly lower at 20 mW/cm^2. The results for the remaining protocols showed no significant RFR-induced alterations in T_4 level except for CR rats given 3 consecutive daily 4-hour exposures at 40 mW/cm^2, for which the T_4 level was significantly lower than for shams.

Lu et al. (1986) sought to determine the influence of confounding factors in studies of effects of RFR on the adrenal cortex. Serum CS concentration was used as the index of adrenocortical function. Groups of acclimated, gentled rats were subjected to 10 protocols involving exposures to 2.45-GHz RFR for 2 or 4 hours at up to 55 mW/cm^2 (11 W/kg). Rises in colonic temperature and CS concentration were found to be dependent on RFR level with distinct thresholds, but the effect diminished with repetition. For example, the threshold for change of CS concentration was 40 mW/cm^2 (8 W/kg) at the first exposure, but rats exposed 10 times at levels up to 40 mW/cm^2 (8 W/kg) showed no changes. Injection of ethanol lowered baseline colonic temperatures and raised CS concentrations, effects not observed for saline-injected controls. Ethanol injection after RFR exposure at 10 or 20 mW/cm^2 yielded higher CS concentrations than in rats injected with saline after exposure. Removal of hair from the rats did not affect the baseline colonic temperatures and CS concentrations significantly, but it decreased RFR-induced hyperthermia and CS stimulation. The authors concluded that no adrenal response to RFR is evident without a colonic temperature rise of at least 0.7-^{o}C (20 mW/cm^2 or 4 W/kg).

Lotz and Podgorski (1982) collected blood samples hourly for 24 hours from 6 rhesus monkeys and assayed them for cortisol, thyroxine (T_4), and growth hormone (GH). At the same clock time during those 24 hours, they exposed each monkey for 8 hours to 1.29-GHz RFR at 20, 28, or 38 mW/cm^2 (2.1, 3.0, or 4.1 W/kg). Three sessions at each RFR level were alternated with sessions of sham-exposure at intervals of 10-14 days for recovery. The data collected for the same clock periods of the three sessions at each RFR level were averaged, to yield a 24-hour temporal series of mean values for each condition.

The mean rectal temperature rose within 2 hours after the start of RFR exposure to plateaus that were dependent on RFR level, but returned to control level within 2 hours after exposure end. For sessions at 20 and 28 mW/cm^2, the mean cortisol levels did not differ significantly from those for sham-exposure sessions, but rose significantly during sessions at 38 mW/cm^2. The levels then diminished to control values, indicating that the effect was transient. The authors suggested the existence of a threshold between 28 and 38 mW/cm^2 (3.0 and 4.1 W/kg) for rises in cortisol levels and associated such rises with rectal-temperature elevations of about 1.7 ^{o}C, thus supporting the hypothesis that adrenocortical effects of RFR are thermally induced. For all RFR levels, no significant differences in mean GH or T_4 levels were seen.

In overall summary, although some effects of RFR exposure on the endocrine system seem to be predictable from physiological considerations, other, more subtle effects may be worthy of additional study, such as those related to the interactions among the pituitary, adrenal, thyroid, and hypothalamus glands and/or their secretions. Part of the problem appears to be related to the uncertainties about stress mechanisms and various accommodations to such mechanisms. Animals placed in novel situations are more prone to exhibit stress responses than those adapted to experimental situations.

Because the effects of RFR on the endocrine systems of animals are largely ascribable to increased thermal burdens, to stresses engendered by the experimental situation, or to both, there is no clear evidence that such effects would occur in humans exposed to RFR at levels that do not produce significant increases in body temperature.

3.6.3 CARDIOVASCULAR EFFECTS

Few investigations were carried out on possible effects of RFR on the human heart. However, various studies were performed *in vitro* on hearts (or parts thereof) excised from animals, and others were done on animal hearts *in vivo*.

3.6.3.1 IN VITRO STUDIES

Frey and Seifert (1968) exposed 22 excised beating frog hearts to 10-μs pulses of 1.425-GHz RFR at 60 mW/cm^2 peak. The pulses were triggered at the peak of the P wave of the electrocardiogram (EKG) and at 100 and at 200 ms after the peak, so the average power density was negligible. The results for zero and 100-ms delays were inconclusive, but a significant increase in heart rate (tachycardia) was seen for the 200-ms delay.

Clapman and Cain (1975) tried to obtain the results above. They exposed 3 of 14 groups of frog hearts to the 1.425-GHz pulsed RFR, but each group was triggered at only one of the delays. Three other groups were exposed with 15-μs instead of 10-μs pulses. The other 8 groups were exposed to 3-GHz RFR at 5,500 mW/cm^2 peak, using 10-μs or 2-μs pulses. For one 2-μs group, the pulses were triggered at the initial rise of the QRS complex of the EKG and another group was exposed to unsynchronized pulses at 500 pps (5.5 mW/cm^2 average power density). No significant differences in heart rate were seen between any of the RFR-exposed groups and a control group, in contrast with the results of the study above.

Liu et al. (1976) also sought effects similar to those of Frey and Seifert (1968), but obtained negative results with excised hearts. They also opened the thorax of frogs and exposed the heart *in situ* to 100-μs pulses of 1.42-GHz or 10-GHz RFR, with negative results.

Galvin et al. (1981b) isolated cardiac muscle cells from the quail heart and exposed them in suspension to 2.45-GHz RFR at 37 ^{o}C for 90 minutes at SARs of 1, 10, 50, or 100 W/kg. After exposure, samples of the suspensions were examined for integrity of the cells. (Intact cells exclude trypan blue,

a vital stain.) The remainder of each suspension was centrifuged and the liquid therefrom (supernatant) was assayed for the release of the enzymes creatine phosphokinase (CPK) and lactic acid dehydrogenase (LDH). The residue pellets from the centrifugation were resuspended and assayed for bound enzyme. Some pellets were examined by electron microscopy.

Cardiac-cell integrity was unaffected by exposure at 1 W/kg, but the suspensions exposed at 10, 50, and 100 W/kg showed successively larger increases in percentages of cells permeable to trypan blue relative to their respective control suspensions. CPK release was unaffected at any SAR. Release of LDH increased with SAR, but the increases relative to the controls were statistically nonsignificant except at 100 W/kg. By electron microscopy, the structural appearance of heart cells exposed at 1, 10, and 50 W/kg, as well as control cells, appeared normal. However, cells exposed at 100 W/kg showed increased intracellular changes, but the intercellular junctions remained intact.

Yee et al. (1984) were concerned about possible electrode artifacts, so they distributed 102 isolated frog hearts in physiological (Ringer's) solution into ten groups, and exposed each heart to 2.45-GHz RFR at 2 or 8.55 W/kg. Heart rates were recorded for each group with one of the following: a glass electrode filled with a potassium-chloride solution, an ultrasound probe, a tension transducer, a glass electrode filled with Ringer's solution, and a metal wire within the glass electrode containing Ringer's solution. Faster than normal decreases in heart rate were seen only in those groups recorded with the potassium-chloride or metal-wire electrodes; no effect was found in the other groups. Those results show that electrode-caused field intensification can induce bradycardia.

Yee et al. (1986) divided 81 frog hearts into 10 groups. After each heart was excised and immersed in Ringer's solution to remove any blood clots, its arteries were tied to prevent washing out of neurotransmitters at the nerve endings. Each heart was mounted within a waveguide filled with Ringer's solution. One group served as controls, eight groups were exposed to 2.45-GHz RFR, and one group was heated by circulation of hot Ringer's solution through the waveguide. The beat rate of each heart was monitored for 60 minutes at 5-minute intervals. For the hearts exposed to RFR, exposure was begun 10 minutes into the monitoring period and was terminated 30 minutes later. The groups were treated as follows:

Group A comprised the controls. The hearts in Group B were exposed individually to 10-μs pulses at 100 pps in 0.5-second trains of 50 pulses, with each train triggered by the EKG; the average SAR was 8.55 W/kg during each train. Group C was similarly exposed, but to random 0.5-second trains not triggered by the EKG. Group D was exposed to EKG-triggered trains, but at 2 W/kg. Group E was exposed to 10-μs pulses, 100 pps, at 8.55 W/kg, but continuously instead of pulse trains. Group F was also exposed continuously, but at 200 W/kg. Group G was continuously exposed at 200 W/kg, but was cooled by circulating bathing solution. Hot circulating bathing solution was used instead of RFR to treat Group H.

The authors noted that Schwartz et al. (1983) had reported a 19% increase in calcium efflux from isolated frog hearts exposed for 30 minutes to

16-Hz-modulated, 1-GHz RFR at 0.15-3 W/kg, an effect not observed for CW RFR or RFR amplitude-modulated at natural heart-beat rates. To investigate that finding, they exposed Groups I and J to CW and pulsed RFR, both amplitude-modulated at 16 Hz, at 3 W/kg average SAR.

The mean heart rate of Group A (controls) decreased linearly to about 67% of initial rate at the end of the 60-minute monitoring period. The decrease for Group B was similar, with no significant differences between the groups at corresponding monitoring times. Similar negative results were obtained for Groups C, D, and E, relative to Group A. The authors remarked that the RFR-induced bradycardia observed by other rsearchers could be ascribed to loss of neurotransmitters via the open arteries, a problem avoided in their experiments by tying the arteries.

Exposure of Group F at 200 W/kg yielded heart-temperature increases of 2.5, 5.5, and 8 ^{o}C respectively at 5, 15, and 30 minutes of exposure; the mean heart rate decreased sharply to about 50% of the initial value by 20 minutes of exposure and decreased further to about 25% at the end of the monitoring period. Group H, heated by bathing solution to yield a temperature-versus-time rise similar to that with RFR, showed a linear decrease in heart rate to final values comparable with those of Group F. By contrast, the differences between Group G, cooled during exposure at 200 W/kg, and Group A were nonsignificant.

The results for Groups I and J, exposed to 16-Hz-modulated CW and pulsed RFR at 3 W/kg, were also not significantly different from those of Group A. The authors remarked that an increase in concentration of free Ca^{++} in the cytoplasm of heart cells triggers rapid changes in heartbeat, so the absence of such changes in Groups I and J does not support the findings of Schwartz et al. (1983).

Yee et al. (1988) did a similar study with rat hearts. However, to avoid arrythmia frequently observed previously in hearts exposed to air at temperatures less than 20 ^{o}C, and to increase the survival time of the excised hearts, the authors used a double circulation system, one part for coronary circulation of Ringer's solution and the other part for circulating Ringer's solution through the waveguide. As in the study of frog hearts, the beat rate of each heart was monitored for 60 minutes at 5-minute intervals, but exposure was begun 20 minutes into the monitoring period and was terminated at 50 minutes.

In control Group A, the solution flowing through the heart was held at 37.7 ^{o}C; the temperature of the waveguide solution was initially at 19 ^{o}C and was increased within 10 minutes to 37.7 ^{o}C and held there for the remainder of the experiment. For this group, mean beat rate increased linearly to a maximum of 70% above initial value at 45 minutes, and then decreased sharply to 40% below initial value at 60 minutes. The hearts of Group B were not exposed to RFR but to air while the Ringer's solution through the coronary was held at 19 ^{o}C. This group frequently exhibited arrythmia and its mean beat rate declined to about 20% of initial value.

Group C was exposed to 10-μs pulses, 100 pps, of 2.45-GHz RFR amplitude-modulated at 16 Hz, at a mean SAR of 2 W/kg, and otherwise treated

the same as Group A. The graph of heart rate versus time for Groups C and A were essentially the same, with no significant differences in heart rates at corresponding times. Group D was treated in the same manner as Group C, but at 10 W/kg. The heart rates also did not differ significantly at corresponding times but were slightly higher than those of Group A for the first 15 minutes of exposure, results ascribed to a small increase in heart temperature (<0.2 ^{o}C).

Group E was exposed at 200 W/kg; it exhibited a sharp increase in mean heart rate during the first 10 minutes of exposure, followed by an abrupt cessation of beating after 20 minutes of exposure. The mean heart temperature rose to 41.7 ^{o}C during exposure, so no RFR was used for Group F, but the temperature of the bathing solution was raised to 41.7 ^{o}C, to approximate the temperature-time profile of Group E. The graph of heart rate versus time of Group F was similar to that of Group E. The authors concluded that exposure to RFR at 2 or 10 W/kg had no specific influence on the myocardium or its neural components.

3.6.3.2 IN VIVO STUDIES

Among the early studies on the live rabbit were two by Presman and Levitina (1963a,b), one with 2.4-GHz CW RFR at 7-12 mW/cm^2 and the other with 3-GHz pulsed RFR at 3-5 mW/cm^2 average power density, 4.3-7.1 W/cm^2 pulse power density. In both studies, the rabbits were exposed for 20-minute periods each in various aspects. During each exposure and for 10 minutes before and afterward, the EKGs of the rabbits were recorded with plate electrodes. The rabbits were sham-exposed once each before and after the series of RFR exposures.

Exposing the entire dorsal surface produced neither tachycardia nor bradycardia during exposure. However, tachycardia was seen during the first half of the postexposure period, changing to bradycardia toward the end of that period. By contrast, dorsal exposure of the head only or of the back only produced significant tachycardia during exposure, with head exposure yielding the greater effect. Tachycardia rose to maximum values about 5 minutes postexposure and then declined to nonsignificant values. Bradycardia was seen during exposure in three ventral aspects; it persisted to exposure end and was followed by returns toward normal rates during postexposure. The effect was most pronounced and was manifested earliest for exposure of only the head.

The findings of those two papers were difficult to assess because no actual data were given, only the relative differences among mean values. Also, use of metal electrodes to record heart-beat data may have introduced artifact, rendering the findings questionable.

Kaplan et al. (1971) and Birenbaum et al. (1975) tried to repeat those studies. Their findings were negative except for RFR levels that were clearly hyperthermic.

Phillips et al. (1975) exposed rats to 2.45-GHz RFR for 30 minutes at 0, 4.5, 6.5, or 11.5 W/kg. Nonsignificant bradycardia was seen at 4.5 W/kg; mild but significant bradycardia developed within 20 minutes at 6.5 W/kg,

followed by recovery in 2 hours; pronounced bradycardia occurred abruptly at 11.1 W/kg, after which heart rates rose to values well above those of controls and persisted at the higher levels to the end of the test period. For most of the rats exposed at 11.5 W/kg, the bradycardia was accompanied by irregular heart rhythms. Incomplete heart block was evident, but with recovery within 60 minutes after exposure cessation. The authors surmised that the heart block was caused by the release of toxic materials, elevated serum potassium, or myocardial ischemia, all from excessive heat.

Galvin and McRee (1981a) studied the effect of RFR exposure *in vivo* on the functioning of the cat heart with and without myocardial ischemia (MI). The MI was produced surgically by occlusion of a coronary artery. One group of MI hearts was exposed to 2.45-GHz CW RFR at 30 W/kg with an applicator for 5 hours, and another MI group was sham-exposed. At this RFR level, heart temperature of dead cats rose at an initial rate of 0.43 ^{o}C per minute, but no increases in aortic blood temperature occurred in live cats. For comparison, two groups of non-MI hearts were similarly treated. Before and during the treatment, mean arterial blood pressure, cardiac output, heart rate, and EKG were measured, and blood samples were assayed for plasma protein concentration and creatine phosphokinase (CPK) activity. After the treatment, the hearts were excised and assayed for tissue CPK activity.

The results for both the MI and non-MI cats showed no significant differences in mean arterial blood pressure, cardiac output, or heart rate between RFR-exposed and sham-exposed groups, and no synergism of ischemia and RFR exposure for those cardiovascular indices. The RFR and sham groups yielded no significant differences in either plasma or tissue CPK activity. Thus, localized exposure of the undamaged or ischemic heart to the RFR *in vivo* had no effect on the myocardium or its neural components, results at variance with those for excised hearts exposed to RFR.

Galvin and McRee (1986) studied the effects of exposure to 2.45-GHz CW RFR at 10 mW/cm^2 (3.7 W/kg) on conscious rats, including cardiovascular, biochemical, and hematologic indices. The rats were individually exposed ventrally for 6 hours in an anechoic chamber. Before treatment, the right femoral artery of each rat was cannulated under anesthesia to permit the continuous recording of mean arterial blood pressure and for removing blood samples. Following surgery, the leg wound was sutured and infiltrated with Lidocaine and the rat was allowed to recover for 2 hours, during which stable heart rate, blood pressure, and colonic temperature were usually achieved.

There were no significant differences between RFR-exposed and sham-exposed rats in any of the blood parameters assayed. Initial mean heart rates of the RFR and sham groups did not differ significantly. However, the mean heart rate of the RFR group decreased, during the first hour of exposure, to about 90% of its initial value, a significant drop, and remained there (with smaller variations) during the rest of the period.

The occurrence of bradycardia led the authors to study another group of rats. The rats were exposed to the RFR for 2 hours and monitored for 2 hours after exposure cessation. Those rats also exhibited bradycardia after the first hour of exposure, but heart rates returned to preexposure values during the postexposure period (no data presented). The authors noted that

the bradycardia was small, and they surmised that it was due to reduction of metabolic rate to compensate for the heat from the RFR.

3.6.3.3 SUMMARY

Frey and Seifert (1968) exposed excised beating frog hearts to 10-μs pulses of 1.425-GHz RFR at 60 mW/cm^2 peak. The pulses were triggered at the peak of the electrocardiogram (EKG) P wave and at 100 and 200 ms after the peak. The results for zero and 100-ms delays were inconclusive, but a significant rise in heart rate (tachycardia) was seen for the 200-ms delay.

Clapman and Cain (1975) were unable to obtain those results. They also exposed groups of frog hearts to 2-μs or 10-μs pulses of 3-GHz RFR at 5,500 mW/cm^2 peak; for one 2-μs group, the pulses were triggered at the initial rise of the EKG's QRS complex and another 2-μs group was exposed to unsynchronized pulses at 500 pps (5.5 mW/cm^2 average power density). Again, no significant differences in heart rate were seen between any of the RFR-exposed groups and a control group, in contrast with those of Frey and Seifert (1968). Liu et al. (1976) also sought similar effects, but obtained negative findings with excised hearts. In addition, they opened the thorax of frogs and exposed the heart *in situ* to 100-μs pulses of 1.42-GHz or 10-GHz RFR, with negative results.

Galvin et al. (1981b) isolated cardiac muscle cells from the quail heart and exposed them in suspension to 2.45-GHz RFR at 37 ^{o}C for 90 minutes at SARs up to 100 W/kg. After exposure, samples of the suspensions were examined for integrity of the cells by their exclusion of trypan blue, a vital stain. Cell integrity was unaffected by exposure at 1 W/kg, but suspensions exposed at 10, 50, and 100 W/kg yielded successively larger increases in percentages of cells permeable to trypan blue relative to control suspensions. Suspensions were assayed for release of the enzymes creatine phosphokinase (CPK) and lactic acid dehydrogenase (LDH). CPK release was unaffected at any SAR. Release of LDH increased with SAR, but the increases relative to the controls were statistically nonsignificant except at 100 W/kg. By electron microscopy, the structural appearance of heart cells exposed at 1, 10, and 50 W/kg, as well as control cells, was normal. Cells exposed at 100 W/kg showed increased intracellular changes, but the intercellular junctions remained intact.

Yee et al. (1984), concerned about possible electrode artifacts, tested several types of electrodes for recording beat rates from isolated frog hearts during RFR exposure. Faster than the usual decreases in heart rate after excision were seen only with glass electrodes containing either potassium chloride or a metal wire, results showing that bradycardia can be induced by field intensification caused by such electrodes.

Yee et al. (1986) mounted isolated frog hearts individually within a waveguide filled with physiologic (Ringer's) solution. The beat rate of each heart was monitored for 60 minutes at 5-minute intervals. For those exposed to RFR, exposure was begun 10 minutes into the monitoring period and was terminated 30 minutes later. At the end of the monitoring period, the mean heart rate of the group of control hearts decreased linearly to 67% of the initial rate.

Other groups were exposed to trains of 10-μs 2.45-GHz pulses at SARs up to 200 W/kg, either triggered or not triggered by the EKG. Most of the RFR-exposed groups exhibited decreases in heart rates similar to those of the controls. Noteworthy were the results for two groups exposed to RFR, both continuously at 200 W/kg, but only one cooled by circulating bathing solution. The uncooled group yielded heart-temperature increases of 2.5, 5.5, and 8 ^{o}C at 5, 15, and 30 minutes of exposure, with concomitant decreases in mean heart rate relative to controls. By contrast, the cooled group showed no significant differences from controls. Moreover, a group heated with circulating bathing solution to obtain a temperature-versus-time rise similar to the 200-W/kg group showed a linear decrease in heart rate to final values comparable to those of that group.

The authors noted that Schwartz et al. (1983) had reported a 19% increase in calcium efflux from isolated frog hearts that were exposed for 30 minutes to 16-Hz-modulated, 1-GHz RFR at 0.15-3 W/kg, an effect not observed for CW RFR or RFR amplitude-modulated at natural heart-beat rates. To investigate that finding, they exposed one group each to CW and pulsed RFR, both amplitude-modulated at 16 Hz, at 3 W/kg. The results did not significantly different from those for controls. The authors remarked that an increase in concentration of free Ca^{++} in the cytoplasm of heart cells triggers rapid changes in heartbeat, so the absence of such changes in these groups does not support the findings of Schwartz et al. (1983).

Yee et al. (1988) did a similar study with rat hearts. As in the study of frog hearts, the beat rate of each heart was monitored for 60 minutes at 5-minute intervals, but exposure was begun 20 minutes into the monitoring period and was terminated at 50 minutes. The results led the authors to conclude that exposure to pulsed 2.45-GHz RFR at 2 or 10 W/kg had no specific influence on the myocardium or its neural components.

Presman and Levitina (1963a,b) had done two heart studies on the live rabbit, one with 2.4-GHz CW RFR at 7-12 mW/cm^2 and the other with 3-GHz pulsed RFR at 3-5 mW/cm^2 average power density, 4.3-7.1 W/cm^2 pulse power density. In both, rabbits were exposed for 20-minute periods each in various orientations. During each exposure and for 10 minutes before and afterward, the EKGs of the rabbits were recorded with plate electrodes.

Exposing the entire top surface produced neither tachycardia nor bradycardia during RFR exposure. However, tachycardia was seen during the first 5 minutes postexposure, changing to bradycardia during the remaining 5 minutes postexposure. By contrast, exposure of the top of the head only or of the rear only produced significant tachycardia during exposure, with the head exposure yielding the greater effect. On the other hand, exposure of the underside of the rabbit yielded bradycardia during exposure, which was followed by returns toward normal heart rates during postexposure. These findings were difficult to assess because no actual data were given, only relative differences among mean values. Also, artifact may have been introduced by the use of metal electrodes.

Kaplan et al. (1971) and Birenbaum et al. (1975) tried to reproduce the results of those studies. Their findings were negative except for RFR levels that were clearly hyperthermic.

Phillips et al. (1975) exposed rats to 2.45-GHz RFR for 30 minutes at 0, 4.5, 6.5, or 11.5 W/kg. Nonsignificant bradycardia was seen at 4.5 W/kg; mild but significant bradycardia developed within 20 minutes at 6.5 W/kg, followed by recovery in 2 hours; pronounced bradycardia occurred abruptly at 11.1 W/kg, after which heart rates rose to values well above those of controls and persisted at the higher levels to the end of the test period. The authors surmised that the heart block was caused by release of toxic materials, elevated serum potassium, or myocardial ischemia, all from excessive heat.

Galvin and McRee (1981a) studied the effect of RFR exposure *in vivo* on the functioning of the cat heart with and without surgically produced myocardial ischemia (MI). One group of MI hearts was exposed to 2.45-GHz CW RFR at 30 W/kg with an applicator for 5 hours, and another MI group was sham-exposed. For comparison, two groups of non-MI hearts were similarly treated. Before and during the treatment, mean arterial blood pressure, cardiac output, heart rate, and EKG were measured, and blood samples were assayed for plasma protein concentration and creatine phosphokinase (CPK) activity. After the treatment, the hearts were excised and assayed for tissue CPK activity.

The results for both the MI and non-MI cats showed no significant differences in mean arterial blood pressure, cardiac output, or heart rate between RFR-exposed and sham-exposed groups, and no synergism of ischemia and RFR exposure for those cardiovascular indices. Also, the RFR and sham groups showed no significant differences in plasma or tissue CPK activity. Thus, localized exposure of the undamaged or ischemic heart to the RFR *in vivo* had no effect on the myocardium or its neural components, results at variance with those for excised hearts exposed to RFR.

Galvin and McRee (1986) exposed conscious rats individually from below for 6 hours to 2.45-GHz CW RFR at 10 mW/cm^2 (3.7 W/kg) and assayed various cardiovascular, biochemical, and hematologic indices. There were no significant differences between RFR-exposed and sham-exposed rats in any of the blood parameters. The initial mean heart rates of the two groups did not differ significantly. However, the mean heart rate of the RFR group decreased to about 90% during the first hour and remained there (with smaller variations) during the rest of the period. Based on the results of a followup experiment, the authors surmised that the bradycardia was due to reduction of metabolic rate to compensate for the heat from the RFR.

In overall summary, there are scientifically credible experimental data to show that the thermoregulatory systems of nonhuman primates can readily compensate for high RFR levels, a finding most significant with regard to possible physiological hazards of human exposure to RFR. This finding is especially important because of the greater anatomical and physiological similarities between human and nonhuman primates than between humans and any other species.

Most of the studies of possible effects of RFR on endocrine systems were conducted on rodents. Studies that reported positive findings also yielded indications that the effects were largely due to increases in the thermal burdens of the animals. In many studies, observed alterations in endocrine function may have been significantly influenced by stresses in the

animals. For this reason, the results of those studies that involved stress reduction by acclimating animals to handling and the experimental situation are notable. Nevertheless, some of the more subtle effects are worthy of further study.

Regarding cardiovascular effects, the positive findings reported in early studies (bradycardia, tachycardia, or both) were suspect because of the use of attached or indwelling electrodes that probably introduced artifact. Various kinds of electrodes were investigated, and special types were developed that were not perturbed by RFR or did not perturb the local RFR fields. Studies involving use of such electrodes showed that heart rates were altered only at RFR levels that produced rises in temperature or otherwise added thermal burdens to the animal.

Also investigated was the possibility that pulsed RFR at repetition rates synchronous with various periodic characteristics of the EKG could alter heart rate. The authors of an early study reported induction of tachycardia in isolated frog hearts by RFR pulses in synchrony with the EKG, but others could not confirm this finding either in isolated hearts or in live animals.

Several researchers showed that for CW RFR, levels well in excess of 1 mW/cm^2 or 1 W/kg were necessary for significant alterations of heart rate. Small bradycardia levels were seen in equilibrated conscious rats exposed for 6 hours at 3.7 W/kg, a finding ascribed to a compensating reduction in metabolic rate. The results of another study indicated that functioning of hearts damaged from other causes (e.g., rendered ischemic) is not affected by exposure to CW RFR at 10 mW/cm^2 or lower.

3.7 BEHAVIOR

Numerous studies have been done on possible effects of RFR exposure on various kinds of animal behavior. Representative papers on this topic have been selected and are discussed in Section 3.7.1 below. Possible interactive effects of exposure to RFR and drugs on the behavior and physiologic responses of animals are discussed in Section 3.7.2.

3.7.1 RFR EFFECTS ON NATURALISTIC BEHAVIOR, REFLEX ACTIVITY, LEARNING, AND PERFORMANCE OF TRAINED TASKS

3.7.1.1 RODENTS

Justesen and King (1970) trained food-deprived rats to lick a nozzle 40 successive times to obtain a drop of dextrose-water solution. The authors then exposed the rats within a modified commercial microwave oven to 2.45-GHz RFR at levels up to 1.5 mW/cm^2 (4.6 W/kg) in 1-hour sessions comprised of alternating 5-minute intervals of RFR and no RFR. The task was rendered more complex with an audio tone, with "tone-on" or "tone-off" presented at random intervals during a session as a signal of reward availability.

The mean number of responses by the rats diminished with increasing RFR level, but the decreases at higher levels were related to cessation of

responding rather than lower licking rates, most likely associated with warming.

In a three-part study, Hunt et al. (1975) exposed rats to 2.45-GHz RFR in a holder within a modified microwave oven for 30 minutes. In the first part, each rat was sham-exposed or exposed to the RFR at 6.3 W/kg, after which it was placed in a chamber in which its exploratory movements were recorded. The mean activities after either treatment decreased with time, but the values were generally lower during most of the period after RFR exposure than after sham-exposure and became comparable for the two treatments toward session end. The RFR-exposed rats were frequently seen sleeping during middle parts of sessions.

In the second part, rats were trained to swim a 6-meter channel forth and back repeatedly during a 24-hour period, with rests of 20-30 seconds at each end of the channel. Each rat's performance versus time was scored as its median swim speed for each successive block of 20 traverses. After training, the rats were given a pretreatment test and distributed into RFR and sham groups on the basis of equal proficiency.

In the first of three experiments in this second part, rats were sham-exposed or exposed at 6.3 W/kg for 30 minutes and tested right after treatment to determine any prompt effects. In the other two experiments, the RFR level was 11 W/kg and the rats were tested right after treatment or after 1-day delay.

The performance of the 6.3-W/kg group was similar to that of their sham group for about 200 traverses, but was below mean control speed for about the next 100 traverses, after which both groups again performed comparably. Colonic temperatures measured right after treatment showed that those exposed at 11 W/kg were rendered severely hyperthermic (41 ^{o}C or higher), with partial relief by immersion for those tested right after exposure. At 11 W/kg, the performance of the group tested right after exposure was clearly impaired by the hyperthermia despite the partial relief from immersion. However, the 11-W/kg group tested 1 day later showed recovery from the hyperthermia, and yielded results similar to those of the 6.3-W/kg group.

In the third part of the study, water-deprived rats were trained to press a lever in a complex vigilance-discrimination task to obtain 0.08-ml quantities of saccharin-flavored water. After stable performance was achieved, each rat was tested on five successive days. On the first day, all were sham-exposed. In the next four days, each group was exposed for one 30-minute period each at 6.5 and 11 W/kg and two of sham-exposure. Performance was tested for 30 minutes right after each treatment, and the results were expressed as percentage errors of omission and commission versus elapsed time at 5, 15, and 25 minutes of testing.

For the test sessions following sham-exposures, the mean omission errors were in the 10-15% range at all three times. For the session after exposure at 6.5 W/kg, the mean of omission errors was 36% at 5 minutes, but dropped to the sham-exposure range at 15 and 25 minutes. After exposure at 11 W/kg, however, the percentages were all much higher than sham-exposure values.

There were no significant differences in mean commission-error results among treatments.

Monahan and Ho (1976) described experiments to determine whether mice would orient themselves so as to minimize absorption of RFR under conditions that did not allow them to escape. Each mouse was exposed for 15 minutes in a holder that permitted relatively free movement within a waveguide system to 2.45-GHz CW RFR at forward powers in the range 0.4-4.8 W in an ambient temperature held at 24 ^{o}C by air flow through the waveguide. The mean SAR and the percentage of forward power absorbed were measured at 5-minute intervals. In a second experiment, exposures were limited to 10 minutes, and the absorptions were recorded at 12-second intervals. The mice could not be watched within the waveguide, but the results of both experiments showed that they oriented themselves to reduce their percentages of RFR energy absorbed and SARs when the forward power was about 1.7 W (initial SAR 28 W/kg) or higher (at 24 ^{o}C).

Lin et al. (1977) sham-exposed or exposed food-deprived rats to 918-MHz RFR at 10, 20, or 40 mW/cm^2 (2.1, 4.2, or 8.4 W/kg) in 30-minute sessions. The rat holder was a truncated cone of rods designed to allow the rat to poke its head through the narrower end and move it freely. A small upward head movement interrupted a horizontal light beam. The rat was required to execute 30 such movements rapidly and regularly for a food pellet. A downward movement gave access to the pellets delivered.

The baseline cumulative responses versus time for three rats showed virtually uniform rates. One of those rats was exposed for 30 minutes each at 2.1, 4.2, and 8.4 W/kg on consecutive days, another was exposed at the same levels on alternate days, and the third was given 30-minute sessions of sham-exposure. No significant performance-rate changes were seen at 2.1 or 4.2 W/kg. At 8.4 W/kg, the first rat's performance did not change for the first 5 minutes, at which time its rate dropped to almost zero; the second rat performed at baseline rate for the first 5 minutes, at a slowly decreasing rate for the next 15 minutes, and then ceased performing for the remaining 10 minutes. Both showed heat stress, including panting, fatigue, and foaming of the mouth.

Another rat was exposed in increments of 3 mW/cm^2 (0.63 W/kg) up to 32 mW/cm^2 (6.7 W/kg), at which level it exhibited similar signs of heat stress. At that level, its response rate remained at baseline for about the first 13-14 minutes, diminished slightly during the next 5-6 minutes, and then dropped significantly for the rest of the session. The results appear to be straightforward and indicate the existence of a threshold between 30 and 40 mW/cm^2 (6.3 and 8.4 W/kg) at 918 MHz for that task.

Computerized thermography was used in the study above to determine energy absorption rates in rat carcasses. An important general finding was the large spatial range of local SARs. As the authors noted, high values of local SAR ("hot spots") could occur from exposure to RFR at seemingly thermally insignificant power densities.

Schrot et. al. (1980) exposed three rats to pulsed 2.8-GHz RFR at average power densities in the range 0.25-10 mW/cm^2 (0.04-1.7 W/kg), and

observed their behavior acquisition. The test apparatus was a standard two-lever rat chamber augmented with a third lever. Each rat was trained to respond to auditory stimuli with chains of presses on the three levers until a predetermined sequence of four presses of the three levers was learned. Each rat was required to learn a different four-member chain of responses during each session. Just before behavior assessment, the rats were sham-exposed or exposed at one of the RFR levels for 30 minutes. The sessions were conducted daily, 5 days a week, and were terminated after 150 reinforcements or 2 hours, whichever occurred first.

Pre-session exposure at 10 mW/cm^2 (1.7 W/kg) of all three resulted in higher error-responding rates, lower sequence-completion rates, and alteration in the normal acquisition pattern. Similar effects were seen at 5 mW/cm^2 (0.7 W/kg) but to a lesser extent. Below 5 mW/cm^2, most data points were within the control range, but a few were outside that range. The significance of the latter points is uncertain.

Gage and Guyer (1982) trained rats to perform on a reinforcement schedule in which the opportunity to obtain a food pellet was presented on the average of once each minute in a preplanned sequence of intervals without cueing. The rat lost a reinforcement opportunity if it did not respond before the next opportunity. After training, groups were exposed to 2.45-GHz RFR for 15.5 hours at 8 or 14 mW/cm^2 (1.6 or 2.8 W/kg) and 22, 26, or 30 ^{o}C ambient temperature without access to food or water. The rats were given water for 10 minutes after treatment, after which the test sessions were begun. The response rates at each ambient temperature diminished directly with increasing RFR level, but the effects of ambient temperature per se were not consistent.

Lebovitz (1981), concurrently sham-exposed and exposed groups of 15 rats to circularly polarized 1.3-GHz pulsed RFR (1-μs pulses at 600 pps) unrestrained in individual waveguides. Within each waveguide were a vertical displacement bar (behavioral operandum), a means for illuminating the operandum as a cue (visual discriminative stimulus), and means for delivering a food pellet. The rats faced the RFR source during operant performance.

Prior to exposure, groups of 46 rats each were initially deprived of food for 2 days and trained for 10 days to press the bar for food pellets at increasing fixed-ratio (FR) schedules to FR-5 (requiring 5 successive lever presses for a pellet). The 30 rats of each group that performed at the highest and most stable rates were selected and trained on a multiple fixed-ratio, extinction schedule of reinforcement that involved visual discriminative stimuli, in which only the responses when an operandum was illuminated (SD) were reinforced by pellet delivery. Such responses were tabulated. Reinforcements were done on a fixed-ratio schedule that was gradually increased to FR-25 during several weeks of training. Responses when the operandum was not illuminated (Sd), which yielded no pellets, were tabulated separately.

Each set of 30 rats that achieved high and steady performance at FR-25 was given a baseline period of sham-exposures and testing, after which half were randomly assigned to the RFR group and half to the sham group, with the two groups matched by baseline FR-25 performance. RFR exposures and sham-exposures were for 3 hours daily, 5 days a week. The behavioral sessions were

begun 15 minutes after exposure start and were terminated 15 minutes before exposure end, for a 150-minute session duration. The rats were also tested during a 2-week recovery period after the exposure regimen. Each behavioral session was divided into 6 sequential blocks of 25 minutes each; each block consisted of a 15-minute SD interval (with the operandum illuminated) followed by a 10-minute Sd interval (operandum illumination extinguished). The response rates of each rat for SD and Sd during baseline, exposure, and recovery periods were summed weekly by block number, and the results for the rats in each group were averaged.

One group each was exposed at 1.5, 3.6, and 6.7 W/kg (3.9, 9.2, and 17.2 mW/cm^2 average; 6.4, 15.4, and 28.7 W/cm^2 peak). When the rats were not in their waveguides, they were held in their home cages with water available ad libitum. Also, each rat was given 8 grams of food daily irrespective of its operant performance, and was weighed three times per week. All rats maintained satisfactory growth curves.

Results for 8 weeks of sham-exposure and exposure at 1.5 W/kg (3.9 mW/cm^2) showed stable response rates and no significant SD differences between RFR and sham groups for corresponding blocks and weeks. Modest declines in rates during sessions (blocks 1-6) were seen in both groups. The response rates for Sd were more variable than for SD. The decline in Sd rates during sessions, which was also evident for the baseline and recovery weeks, was sharper than for SD, but there were no significant differences between the RFR and sham groups.

Groups sham-exposed and exposed for 9 weeks at 3.6 W/kg (9.2 mW/cm^2) also showed no significant differences in SD response rates. There were marginally significant changes in the weekly rates and the intrasession decline in rate was significant. For the Sd response rates (which again showed sharp intrasession declines for both groups), analysis revealed an apparently transient difference between groups: the Sd response rate by the RFR group was significantly lower than for the sham group only for blocks 2 and 3 of the first exposure week. The author remarked that similar results were obtained with another group of rats exposed at the same RFR level.

Results for 6 weeks of exposure at 6.7 W/kg (17.2 mW/cm^2) showed no significant differences between groups in overall SD response rates, but there were significant block-dependent differences between groups. In particular, the RFR group's block-6 SD rate was significantly lower than the sham group's rate for week 2, and was marginally significantly lower for weeks 1, 3, and 4. The differences were ascribed to reductions in bar pressings near the end of behavioral sessions (blocks 4-6) during those weeks. An analysis by rat showed that the differences between SD rates during the last baseline week and the first exposure week were not significant, showing that the decline was gradual rather than immediate.

Also at 6.7 W/kg (17.2 mW/cm^2), the Sd rates showed significant intrasession declines for both groups during the baseline period, with nonsignificant intergroup differences. For unknown reasons, however, the Sd rates of both groups varied up and down during sessions, rendering it difficult to interpret the results. The block-6 rates of both groups were already low during the baseline period, but the RFR group's rate dropped to

almost zero during exposures, with only slight increases seen during the recovery period.

Based on the negative results for SD and Sd at 1.5 W/kg and the doubtfully significant decline in Sd rate at 3.6 W/kg, the author suggested that the latter RFR level could be the approximate threshold for modifying the rate of operant responding in the absence of visual cues or food reinforcement.

The author also indicated that 6.7 W/kg is the approximate resting metabolic rate for a 240-g rat, so such RFR exposure represented virtual doubling of the heat dissipation requirements of the rat. He therefore concluded that thermal factors were likely involved in the behavioral effects. By his calculation, the energy deposited in the rat during each pulse exceeded the threshold for the RFR-auditory effect, but questioned whether the loudness perceived by the rat would constitute an adequate acoustic cue or how the presence of such a cue could account for the observation that the major decline in Sd responding was gradual rather than immediate with the onset of RFR exposure. He then indicated that other studies with CW RFR yielded essentially the same findings.

As noted, the operant data for each rat consisted of the number of bar presses during each of the 6 blocks or pairs of cued (SD) and uncued (Sd) response intervals sequentially numbered 1-6 daily. However, not clear was the rationale for summing the responses for correspondingly numbered blocks to obtain weekly block SD and Sd response totals as the "primary descriptive variables" for each rat, and why the time-dependent data for the successive blocks during daily sessions were not described or treated more explicitly, since even the baseline SD and Sd rates both exhibited intrasession diminutions. Thus, it is difficult to assess the contribution of this time-dependent non-RFR factor despite the extensive statistical treatment.

Lebovitz (1983) sham-exposed or exposed trained groups of 15 rats each to CW or pulsed 1.3-GHz RFR (1-μs pulses at 600 pps). As in the previous study, the rats were trained to press the bar for pellets at increasing fixed-ratio schedules to FR-5, and then were trained daily on a multiple schedule that started with a 15-minute interval (called S+ instead of SD) of bar illumination and pellet availability at FR-25, followed by a 10-minute time-out interval (called S- instead of Sd) of no illumination or pellet availability. Each session consisted again of six contiguous pairs of S+ and S- (25-minute periods) numbered 1-6.

After a week of baseline performance by two groups, one was exposed to CW RFR at 5.9 W/kg (15.2 mW/cm^2) and the other was sham-exposed for a week. For the baseline week, the S+ results for both groups exhibited a trend toward decreasing response rates of 10% from period 1 to period 6 but no significant differences between the groups. During the week of exposure, both groups also showed a downward trend in S+ rates, but the RFR group's decline in response rate was significantly faster.

During the baseline week, the S- response rates of this RFR group were initially higher than for the sham group, but they declined faster between period 4 and period 5, so the S- rates for the two groups were comparable for

periods 5 and 6. During the week of exposure, the sham group exhibited higher rates for periods 1 and 2 than they did for the same periods of the baseline week, and approximately the same rate of decline. However, the rates of the RFR group for periods 1-3 dropped sharply to almost zero for periods 4-6.

For exposure to pulsed RFR at 6.7 W/kg (17.2 mW/cm^2), response rates during both S+ and S- were similar to those with CW RFR at 5.9 W/kg (15.2 mW/cm^2). (Limitations of equipment did not permit closer match of SARs.) The author remarked that the results with pulsed RFR at this level were similar to those obtained in the previous study with pulsed RFR at the same level and that occurrence of similar changes in S+ rates with CW RFR at a comparable SAR showed that the effect was not ascribable to the pulsed character of the RFR.

For a group exposed to CW RFR at 3.6 W/kg (9.2 mW/cm^2), the S+ rates during the baseline week were consistently lower than those for the corresponding sham group, but the rates of decline for periods 1-6 were essentially the same. Similar results were also obtained for the week of exposure except that the initial (period-1) response rates for both groups were higher than the initial rates for the baseline week.

The S- rates of the 3.6-W/kg group were consistently higher than those of the sham group for the baseline week, but with comparable rates of decline, thus yielding no significant differences between the groups. The S- results for the week of exposure showed that the response rates of the RFR group were consistently higher than of the sham group; the response rates of both groups declined for periods 1-6, but the decline was much faster for the RFR group. These results were again consonant with those of the previous study.

Separate groups of 5 rats each were used to determine rises in core temperature due to RFR exposure. Each rat was exposed for 1 hour or 3 hours and its temperature was measured just before it was placed in the waveguide and within 10 minutes after it was removed. Exposures to CW or pulsed RFR at 3.5 W/kg, the approximate threshold for the behavioral effects above, yielded no significant differences in rectal-temperature changes compared with rats similarly sham-exposed. However, exposures at 6.3 W/kg, CW or pulsed, yielded increases of 0.5-1 ^{o}C, with no significant duration-dependent differences.

As was true for the previous study, the engineering aspects were excellent, and the statistical treatment of the data provided a sound basis for the conclusions reached. Moreover, the presentation of the data at 5.9 W/kg (CW) by operant days (a format lacking in the previous paper) provided greater insight into the time-dependent aspects of the results. Especially noteworthy was that the daily S+ response rates for period 1 were not significantly affected by the entire week of exposure to RFR and that the declines in those rates occurred progressively in the subsequent periods of each session. Also more clearly evident were the virtually immediate sharp declines in S- response rates for all periods at the onset of RFR exposure. In the absence of light cue and pellet rewards, it is possible that the rats were thoroughly confused by the presence of the RFR. Another possibility suggested by the author was that without such reinforcement, the rats tried to reorient themselves so as to redistribute the thermal burden added by the RFR.

As indicated by the author, the thermal basis for the behavioral changes is evident, with a threshold of about 3.5 W/kg irrespective of whether the RFR is CW or pulsed. Also, even though the pulse width (1 μs) and peak power density (estimated as about 28.7 W/cm^2) were sufficient to produce the RFR-auditory effect, there was little doubt that perception of the pulses as sound (if it occurred) was not a factor in the results obtained.

D'Andrea et al. (1986a) adapted 28 rats to exposure chambers and divided them into two groups of 14 each. One group was exposed for 7 hours per day on 90 consecutive days, totaling 630 hours, to 2.45-GHz CW RFR at 0.5 mW/cm^2 (0.14 W/kg); the other group was sham-exposed. Body masses and intake of food and water were measured daily. Each rat was tested monthly for its threshold reactivity to footshock by observing its paw movements in response to electric shocks of varied intensity within a gridded-floor chamber. The differences in body masses, food and water intake, or threshold footshock reactivities between the groups were not significant.

After the 90 days of treatment, 7 rats of each group were assessed for open-field behavior, shuttlebox performance, and lever pressing for food pellets on an interresponse time schedule. The remaining 7 rats in each group were euthanized and examined for gross pathology; no significant differences ascribable to the RFR were found in the necropsies. In the open-field tests, each rat was placed in the center square of a floor of 20-cm squares, and its crossings into adjacent squares and its rearings during a 1-minute period on each of three successive days were counted. Major changes were seen in both tests over the daily trials, but no significant differences were ascribable to RFR exposure. The open-field tests 60 days after treatment yielded similar results.

Shuttlebox performance was tested using a tone and white light as a compound conditional stimulus (CS) and electric shock as an unconditional stimulus (UCS). Each rat was trained on trials consisting of presenting the CS for 10 seconds immediately followed by presentation of the UCS. By crossing to the other side of the shuttlebox during the 10 seconds of CS, the rat could prevent presentation of the UCS, a behavior termed an avoidance response. A crossing during a UCS presentation was termed an escape response. The latencies for avoidance and escape responses were recorded. Two days after shuttlebox testing, the rats were deprived of food and trained daily to press a lever twice for a food pellet, with a specific time interval between the presses. The training was rendered more difficult until the rats were required to do the second press only between 12 and 18 seconds after the first press to obtain a food pellet.

The shuttlebox responses were highly variable: four RFR-exposed rats showed relatively long escape latencies and poor avoidance, whereas the other three RFR-exposed rats did as well as those sham-exposed. Overall, the differences were not statistically significant. The shuttlebox test done 60 days after treatment also showed no significant differences in mean latencies or their variances. During training in the interresponse-time tests, the RFR group earned fewer pellets than the sham group, but the differences at corresponding times and overall were nonsignificant.

The results of the study above and of two similar studies in the same laboratory (D'Andrea et al., 1986b; DeWitt et al., 1987) were not fully consistent and exhibited little if any statistically significant differences between RFR-exposed and sham-exposed rats, but suggested that the threshold for behavioral responses to 2.45-GHz RFR in rats may be in the range 0.5-2.5 mW/cm^2 (0.14-0.70 W/kg).

Mitchell et al. (1988) exposed rats from above to 2.45-GHz CW RFR at 10 mW/cm^2 for 7 hours within an anechoic chamber in individual plastic cages that permitted free movement. Concurrently, two cages were exposed to the RFR and two others were sham-exposed in another anechoic chamber, with 10 replications of the experiment (20 each RFR-exposed and sham-exposed rats). Calorimetric measurements with rat carcasses yielded a spatial mean whole-body SAR of 2.7 W/kg, assuming that the rats spent equal times in horizontal orientations parallel and perpendicular to the electric component of the RFR. For 8 days before treatment, the rats were adapted to the chambers for 8 hours daily. Right after treatment, each rat was tested for vertical and horizontal spontaneous locomotor activity, acoustic startle response, and retention of a shock-motivated passive avoidance task.

The vertical and horizontal locomotor activities of each rat were assessed as photoelectric detections of light-beam interruptions during 5-minute intervals of a 30-minute test session. Lower activity was seen in the RFR-exposed rats than the sham-exposed rats, especially during the second half of test sessions.

In the startle-response test, given at the end of the locomotor test session, each rat was subjected to 20 intense 8-kHz, 0.2-second acoustic pulses at variable intervals in the range 20-60 seconds (mean interval 40 seconds), and the response of the rat during each acoustic pulse was determined. The mean of startle responses of the RFR-exposed rats was significantly lower than for the sham-exposed rats.

Immediately after the startle-response test, each rat was placed in the lighted smaller part of a gated, two-chamber shuttle box, the larger part of which was dark and equipped to deliver an electric shock. After 1 minute for adaptation, the gate was opened, and if the rat moved into the larger chamber within 2 minutes, it was given a 1-second shock; if it remained in the smaller chamber for more than 2 minutes, it was removed and not tested further. (Tested were 17 RFR-exposed and 16 sham-exposed rats.) One week later, retention of the shock experience was tested in the box by allowing each rat 5 minutes (instead of 2 minutes) within the smaller chamber to react. The differences in passive avoidance activity between the two groups were not significant.

Akyel et al. (1991) trained 12 rats to press a lever to obtain food pellets. The rats were then trained on reinforcement schedules: 4 rats on a fixed-ratio (FR) schedule, another 4 rats on a variable-interval (VI) schedule, and the remaining 4 rats on a differential-reinforcement-of-low-rates (DRL) schedule.

After training and subsequent adaptation to the exposure chamber, each rat was exposed once a week for 10 minutes to 10-μs pulses of 1.25-GHz RFR at

1-MW peak forward power, with its long axis parallel to the electric component of the RFR. The average forward power was held constant, during any session, at 4, 12, 36, or 108 W, obtained by using a pulse repetition frequency of 240, 720, 2160, or 6480 pps. Each rat was administered all four RFR levels in a weekly quasi-random order. The corresponding whole-body total doses or specific absorptions (SAs), and the whole-body specific absorption rates (SARs) respectively ranged from 0.5 to 14.0 kJ/kg and 0.84 to 23.0 W/kg. Testing of each rat was begun within less than 80 seconds after exposure end.

At the three lower RFR levels, no significant differences in any of the three behavior schedules were seen. At the highest level (14.0 kJ/kg, 23.0 W/kg), however, the rats trained on the FR and VI schedules failed to reach baseline performance, and those on the DRL schedule exhibited variable effects. Exposures at that level caused an average rise in colonic temperature of 2.5 ^{o}C, and the rats did not respond at all for about 13 minutes after exposure completion. The authors concluded that those behavioral changes were thermally induced.

3.7.1.2 NONHUMAN PRIMATES

Galloway (1975) trained rhesus monkeys to press one or more of three levers on panels when the panels were selectively lit in order to obtain food pellets. After training, the head of each monkey was exposed with an applicator to 2.45-GHz RFR at estimated mean head SARs of 7, 13, 20, 27, and 33 W/kg, and the effects on their performance were examined.

For studying discriminative behavior, the RFR was administered for 2 minutes just before each behavioral session but was terminated earlier if the monkey began to convulse. Convulsions occurred for all exposures at 33 W/kg, and often at 20 W/kg. Each monkey was exposed at least twice at each level during a 9-month period. Also, three of them were exposed at 13 W/kg for 5 daily 1-hour schedules of 2 minutes on and 1 minute off, totaling 40 minutes of exposure per day. No effects on discriminative behavior were evident for either exposure regimen.

In a repeated-acquisition test, each monkey had to press the correct lever for each of four illumination stimuli in the proper sequence. An incorrect lever press caused a 15-second timeout, during which any lever press had no effect. Sessions of 60 trials were conducted daily before exposure, with the correct sequence changed each day. In sessions just preceding RFR exposure, a slight learning trend (diminishing error rate) was seen, but the changes were too small to ascribe significance. This was also true for the results at all RFR levels except 33 W/kg, for which the error rate at session start was highest. Thus, except possibly for the latter result, the RFR had no effect on this behavioral paradigm.

Cunitz et al. (1975) trained a 3-kg and a 5-kg rhesus monkey on a four-choice, forced-choice serial reaction program. Each monkey's head was inserted through a hole in the bottom of a 383-MHz resonant cavity, with the monkey facing a diamond array of the ends of four light pipes mounted through the cavity's side wall. Lighting any pipe required the monkey to move a lever to the left, right, up, or down to correspond with the position of that pipe end in the diamond. For criterion performance, 100 correct lever presses were

required to obtain a food pellet. During performance, the light stimuli were presented in random order. A correct response produced an immediate stimulus change and presentation of a tone for 0.75 second. An incorrect response yielded a 3-second timeout during which all lights were off and lever movements had no consequences.

In each session, the monkey was restrained in a chair for 1 hour before the behavioral program was started; the program was then conducted for 1 hour (or halted sooner when the monkey obtained its entire daily food ration). Each monkey was exposed to 383-MHz RFR during the entire 2-hour session at a fixed power input in the range 0-15.0 W. Head SARs were estimated to range up to 33 W/kg and 20 W/kg respectively for the 3-kg and 5-kg monkeys. The larger monkey was also exposed at 17.5 W (23 W/kg). The sessions were conducted on 5 consecutive days at each level, with sham-exposure sessions before the RFR was raised to the next level.

Exposures below 10 W did not alter either monkey's performance. The rate of correct responses of the 3-kg monkey at 10 W (22 W/kg) decreased sharply during exposure days 1-3, and recovered partially on days 4 and 5 and the subsequent sham-exposure sessions. At 15 W (33 W/kg), the drop was very severe (to almost zero on day 5), with recovery to about a third of baseline rates during the subsequent sham-exposure sessions. The 5-kg monkey's performance was not affected significantly at 15 W (20 W/kg). At 17.5 W (23 W/kg), its performance dropped sharply, but recovered to baseline in the subsequent sham-exposure sessions, indicating that the effect was reversible. The lowest head SARs for diminished performance by the two monkeys were about the same: 22 and 23 W/kg.

Scholl and Allen (1979) trained three rhesus monkeys in a visual-tracking task that required each monkey, seated in a restraining chair, to move a lever to hold a continuously moving spot within a prescribed clear area on the screen of a display monitor. The spot was moved electronically in a specific pattern, and the lever responses generated continuous difference signals (errors). The central 15% of the screen was clear and comprised the on-target area. That area was surrounded by a 35% area of light blue, and the remaining 50% area was dark blue. The monkey received a 0.1-second electric shock for each 1 second accumulated outside the clear on-target area.

After training, the monkeys were exposed to horizontally polarized, 1.2-GHz CW RFR at 10 and 20 mW/cm^2 (measured at the center of the head in the absence of the monkey) for 2 hours per day at 2-day intervals until each was exposed for 120 minutes at each level. This polarization and frequency were chosen to provide half-wave resonant absorption in the monkey head. The corresponding head SARs were 0.8 and 1.6 W/kg. Each daily session comprised 40 work trials of 1.5 minutes each, alternating with similar rest periods. Baseline runs were done for 26 consecutive days to ensure performance stability, and the results of the last six runs were used for statistical analysis.

The endpoint scored was the adjusted root mean square (ARMS) of the tracking error for each trial, expressed as a percentage of the total target area. The 95% simultaneous confidence limits were calculated for each monkey's baseline runs, and the ARMS was plotted for each of the 40 trials in

each 2-hour session during RFR exposure at each level. Of 720 data points collected during a total of 36 hours of RFR, only 4 points were outside the confidence limits, fewer than expected by chance. It seems clear that the performance of the monkeys was not diminished by the RFR exposure. Whether the apparent performance improvement observed was RFR-related could not be ascertained.

De Lorge (1976) trained five rhesus monkeys to perform the following task while seated: Each monkey was required to press a lever in front of its right arm, thus producing either a low-frequency tone for 0.5 second to signal that no food pellet will be coming, or a higher-frequency tone for which the monkey had to press a lever in front of its left arm to receive a pellet. Training sessions were for 1 or 2 hours. During 1-hour sessions, pellets were made available at variable intervals (VI) around an average of 30 seconds (VI-30-s schedule). For example, presses of the right lever would yield the high tone once about every 30 seconds and the low tone at other times. During the 2-hour training sessions, pellets were made available on a VI-60-s schedule.

The monkeys were exposed frontally to vertically polarized, 120-Hz-modulated 2.45-GHz RFR at levels in the range 4-72 mW/cm^2 measured at head height. Superposed in some experiments were 0.1-second pulses at 1 pps. Estimated head SARs were 0.4-7.2 W/kg (0.1 W/kg per mW/cm^2).

After stable VI-30-s behavior was achieved, 1-hour sessions were conducted on each monkey, during which the monkey was exposed to the 120-Hz-modulated RFR with superposed 0.1-second pulses at 4 or 16 mW/cm^2 (0.4 or 1.6 W/kg head SAR) for 30 minutes. Similar sessions were conducted with the unpulsed modulated RFR and with no RFR. At either RFR level, the performances of the monkeys were not affected by either the unpulsed or pulsed RFR, which led to the use of only the unpulsed RFR and of the VI-60-s schedule during the 2-hour test sessions. Only three of the monkeys were tested in the 2-hour sessions, during which they were exposed for 1 hour at levels in the range 16-72 mW/cm^2. One of them was also exposed at 16 mW/cm^2 during entire 2-hour test sessions.

The VI-60-s performances showed no significant departures from the control rates for all three monkeys up to 52 mW/cm^2 (5.2 W/kg) and for two of them at 62 mW/cm^2 (6.2 W/kg). The mean performance of the third monkey at the higher level was about 80% of its mean control performance. At 72 mW/cm^2 (7.2 W/kg), all three monkeys performed at approximately 50% of their respective control values. The results suggest that the monkeys had reacted to body heating by the RFR at the higher levels and that their performances were diminished because of such heat.

De Lorge (1979) trained four squirrel monkeys in 1-hour sessions to press either the right or the left lever on top of a chair to obtain a food pellet. Initially, each successive lever press of either lever resulted in turn-on alternately of a red light and a blue light in front of the monkey. When the monkeys achieved consistent performance in such lever presses, the contingencies were changed such that presses of the right lever continued to alternate the red and blue lights (without reward) but a press of the left lever was rewarded only when the blue light was on.

Training progressed in stages, with each stage requiring a higher number of right-lever presses to turn on the blue light. The last stage was a schedule in which each right-lever response yielded either 0.5 second of red light or 10 seconds of blue light, and only a left-lever press during the latter yielded a pellet.

After stable behavior was achieved, each monkey was exposed from above to 2.45-GHz RFR at levels in the range 10-75 mW/cm^2. SARs were estimated to have been 0.5 to 3.75 W/kg. In 41 daily sessions, exposures were done during the middle 30 minutes of 1-hour testing sessions, with the other two 15-minute periods for obtaining baseline data. In the next 53 sessions, only three of the monkeys were tested, the session duration was 2 hours, and the RFR exposures were during the middle 1 hour. The number of sessions at each level ranged from 2 to 5, with sham-exposures between sets. Neither the 30-minute nor the 60-minute exposure regimens caused any obvious permanent physical changes in any of the monkeys.

Among the various performance measures, only the rate of right-lever responses showed an RFR-induced change. This measure exhibited a slight trend toward lower rates with increasing RFR level, to a minimum of about 90% of mean control value at 60 mW/cm^2 (3.0 W/kg), and a slightly higher value (92%) at 70 mW/cm^2 (3.5 W/kg). However, the response rate never exceeded one standard deviation from 100%. The behavioral effects of 1-hour exposures were similar to those of 30-minute exposures but were more pronounced. No consistent behavioral changes occurred below 50 mW/cm^2 (2.5 W/kg); above that level, the effects increased with RFR level. The right-lever-response rate versus RFR level varied widely among the three monkeys, but at 60 mW/cm^2 (3.0 W/kg), all showed decrements to about 60%.

The author concluded that the observed behavioral changes in the squirrel monkeys were temporary and clearly related to hyperthermia. Consistent changes were seen when rises in rectal temperature exceeded 1 ^{o}C, which corresponded to a threshold between 40 and 50 mW/cm^2 (2.0-2.5 W/kg). The author noted that similar results had been obtained with rhesus monkeys tested for the same behavioral task during exposure to 2.45-GHz RFR, but with a threshold 10 to 20 mW/cm^2 higher, and suggested that RFR-induced behavioral changes in different species may be scaled on the basis of body mass.

The findings of this study, reinforced by the similar results with rhesus monkeys, are important because the measurements of performance of a complex behavioral task during exposure to RFR were carried out with two species much closer to human physiology and intelligence than more commonly used non-primate laboratory animals, and because reasonably accurate RFR thresholds for each primate species were determined.

De Lorge (1984) similarly trained food-deprived rhesus monkeys to perform a task in which each monkey was to press a lever in front of its right hand (an observing response), which produced a 0.7-second low tone (860-1000 Hz) to signal that no food pellet will be delivered, or a high tone (1250-3703 Hz) for up to 1.2 seconds to signal the availability of a pellet. If the monkey pressed a lever in front of its left hand while the high tone was on (a detection response), the tone would cease and a pellet would be delivered. A left-lever response at other times produced a 5-second interval during which

presses of the right lever yielded only the low tone. If the left lever were not pressed during 1.2 seconds of the high tone, that tone would cease and the reinforcement schedule would recycle. No tones were presented without a lever press, and right-lever presses during the presence of either tone had no consequences.

The low tone was delivered most frequently and the high tone was sounded at random times at an average of about once every 30 seconds. Reinforcement was at random intervals of about 1 minute initially, and the intervals were shortened as the responses became more efficient.

After several sessions of stable performance, each monkey, while seated in a Styrofoam restraining chair, was frontally exposed, during 1-hour sessions, to vertically polarized 225-MHz CW RFR (near the whole-body resonant frequency), or to pulsed RFR at 1.3 GHz or 5.8 GHz (both above whole-body resonance).

Estimates of normalized SAR were derived from exposure of saline-filled models to 225 MHz and 1.3 GHz, and of models filled with tisue-simulating materials to 5.8 GHz. The results, in W/kg per mW/cm^2, were 0.4 for 225 MHz, 0.13 for 1.3 GHz, and 0.03 for 5.8 GHz. The exposures to 225 MHz were at 5-11 mW/cm^2 (2.0-4.4 W/kg). The 1.3-GHz RFR consisted of 3-μs pulses, 370 pps, at 20-95 mW/cm^2 average (2.6-12.4 W/kg); the 5.8-GHz RFR consisted of 0.5-μs or 2-μs pulses, 662 pps, at 11-150 mW/cm^2 (0.34-4.7 W/kg). Rectal temperature was monitored continuously during each session with a nonperturbing probe.

For each frequency, each monkey was exposed three times at each RFR level, with the levels usually sequenced in ascending order, but all RFR sessions were followed with sham-exposure sessions. Four of the monkeys reduced their rates of incorrect detection responses (on the left lever) to low, stable levels. The fifth, subject 10, made excessive numbers of incorrect detection responses throughout the study, which were sometimes greater than its observing-response rate (on the right lever).

Reductions in observing-response rates occurred at RFR levels above threshold. For example, one monkey (subject 13) exhibited decreases in observing-response rates during exposure to 1.3-GHz RFR at 50 mW/cm^2 and higher, and the rate reduction became larger toward the latter part of each session as the RFR level was raised. Also observed were response patterns that became increasingly erratic during sessions, an effect most pronounced at 225 MHz, at which the monkeys paused for as much as 15 minutes and often stopped responding at all for the last half of a session at 10 mW/cm^2.

As a more definitive index of behavioral change than the individual cumulative records, plots of the mean and standard error of the ratio of observing-responses during each RFR-exposure session at each frequency to the values during the preceding sham-exposure session versus the power density were shown. The results for each frequency yielded a threshold power density for statistically significant behavioral alterations that increased with frequency: 7.5 mW/cm^2 at 225 MHz, 63 mW/cm^2 at 1.3 GHz, and 140 mW/cm^2 at 5.8 GHz. However, the corresponding threshold whole-body SARs varied up and down

with frequency: respectively 3, 8.2, and 4.3 W/kg, presumable because of differences in penetration depth.

Exposure to 5.8-GHz RFR at 150 mW/cm^2, the highest level at that frequency, also produced minor burns on the faces of three of the five monkeys, with the worst burns occurring between the eyes and along the orbitonasal area. The erythema generally disappeared within a few days except in one monkey, which continually irritated the burned skin by removing scabious material. No burns occurred at 140 mW/cm^2 (4.3 W/kg), the behavioral threshold for this frequency, or at the highest power densities for the other frequencies. The small penetration depth for 5.8 GHz (about 0.8 cm) probably was an important factor.

The detection-response rate on the food lever was not consistently affected by RFR exposure at any frequency. No effect was observed for 225 MHz or 5.8 GHz; for 1.3 GHz, a decreased response rate was observed occasionally, but only at 83 mW/cm^2 or higher. However, plots of mean ratio of detection-response latencies during RFR exposure to detection-response latencies during sham-exposure versus power density exhibited values slightly but significantly higher than 1 at all three frequencies and at most power densities. For each frequency, however, the mean ratio changed both upward and downward with power density, but with an overall downward trend.

Post-reinforcement pause (a pause following a reinforced detection-response) was also affected. The mean ratio during exposure to 225-MHz RFR to that during sham-exposure was 1.0 in the range 5-7.5 mW/cm^2, but rose significantly to 1.5 at 10 mW/cm^2. The changes for 1.3 GHz were both upward and downward, but nonsignificant up to 63 mW/cm^2, at which the mean ratio was 1.3. Above 63 mW/cm^2, the mean ratio decreased, to 1.1 at 93 mW/cm^2, the latter ratio still significantly larger than 1.0. The only significant change for 5.8 GHz was at 150 mW/cm^2, to 1.06, a smaller increase than for the other frequencies.

The mean colonic temperature at the start of the 1-hour sessions rose an average of 0.15 ^oC during the sham-exposure sessions. For 225 MHz, the temperature rises were linear with RFR level, from 0.8 ^oC at 5 mW/cm^2 to 2.1 ^oC at 10 mW/cm^2. With 1.3 GHz, the rises were less than linear, from 0.4 ^oC at 20 mW/cm^2 to 1.9 ^oC at 93 mW/cm^2. With 5.8 GHz, the rises were even more gradual, from 0.2 ^oC at 10 mW/cm^2 to 1.0 ^oC at 150 mW/cm^2.

The author's estimates of absolute thresholds for the disruption of observing-response rates for each frequency were 8.1 mW/cm^2 for 225 MHz, 57 mW/cm^2 for 1.3 GHz, 67 mW/cm^2 for 2.45 GHz (from de Lorge, 1976), and 140 mW/cm^2 for 5.8 GHz, values that rose with frequency. However, the corresponding SARs, 3.2, 7.4, 6.7, and 4.3 W/kg, varied both upward and downward with frequency, perhaps reflecting penetration-depth differences again.

The results led the author to remark that predictions of biological effects based only on power density are poor, and that predictions from normalized whole-body absorption of energy are not very useful. He also noted that the ratio of highest-to-lowest threshold SAR is much smaller than the ratio of the corresponding power densities, so SAR is a more efficient

predictor than power density, but that both are frequency-dependent. Thus, he concluded that an increase of about 1 ^{o}C in colonic temperature is a more reliable single index of behavioral disruption.

The author speculated that the 225-MHz results reflect a resonance heating effect of the blood in the entire body, causing great difficulty in thermoregulation, because heated blood cannot be replaced with cooler blood. He also suggested that the results at 1.3 and 5.8 GHz illustrate normal thermoregulation, since the limbs or skin are heated much more at those frequencies than the interior of the head.

Absent was any discussion of the possible occurrence of the RFR-auditory effect with the 1.3-GHz and 5.8-GHz pulsed RFR. The author presumably discounted this effect as a factor in the results, because the pulse repetition rates used (370 and 662 pps) were lower than the tones used in the behavioral paradigm.

D'Andrea et al. (1989) trained five food-deprived rhesus monkeys to operate three levers (left, right, center) in various sequences to obtain food pellets. The sessions were 60 minutes long. The task during each session comprised three successive 10-minute schedules of lever presses, followed by repetition of the same three schedules. About 60 baseline sessions were given before the start of sham- or RFR exposures.

In the first 10-minute schedule, the monkey was required to withhold responding for 8 seconds after the start of a 1,070-Hz tone, and then to respond only within the next 4 seconds; the correct response during those 4 seconds was two presses of the left lever within 2 seconds of each other. The authors called this an interresponse-time (IRT) schedule.

The second 10-minute period was devoted to a time-discrimination (TD) schedule, in which a press of the center lever in the presence of blue light yielded white light of short duration (1-3 seconds) or long duration (8-10 seconds) in random fashion. At the end of either period, the white light was replaced with red and green light. When the red and green light were present, the monkey, to obtain a pellet, had to press the right lever if the preceding white light was of short duration or the left lever if the preceding white light was of long duration.

During the third 10-minute period, a fixed-interval (FI) schedule was used: The monkey was presented with a continuous 2,740-Hz tone, and its first press of the right lever after 55 seconds yielded a pellet.

During the 60-minute behavioral test sessions, each monkey was sham-exposed or exposed from above to 3-μs pulses of 1.3-GHz RFR at a root-mean-square pulse power density of 131.8 W/cm^2. The peak SAR was 15.0 W/kg in the head and 8.3 W/kg whole-body. The pulse repetition rate was 2, 4, 8, 16, or 32 pps, with corresponding average power densities of 0.92, 1.85, 3.70, 7.40, or 14.80 mW/cm^2.

The results showed no significant differences between sham- and RFR exposures in any of the behavioral responses. The authors noted that the the energy absorbed in the head by each pulse (280 mJ/kg) was well above the

threshold for the RFR-auditory effect, and remarked that if such auditory stimulation did occur, it produced no obvious effect on the trained behavior.

3.7.1.3 SUMMARY

Justesen and King (1970) trained food-deprived rats to lick a nozzle 40 successive times to obtain a drop of dextrose-water solution. They then added use of an audio tone presented at random intervals to signal reward availability. After such training, the rats were exposed to 2.45-GHz RFR at up to 1.5 mW/cm^2 (4.6 W/kg) in 1-hour sessions comprised of alternating 5-minute intervals of RFR and no RFR. The mean number of responses by the rats diminished with increasing RFR level, but the decreases at higher levels were related to cessation of responding rather than lower licking rates, most likely associated with warming.

In a three-part study, Hunt et al. (1975) exposed rats to 2.45-GHz RFR for 30 minutes. In the first part, each rat was exposed to the RFR at 6.3 W/kg or sham-exposed, after which its exploratory movements within a test chamber were recorded. The mean activities after either treatment decreased with time, but the values were generally lower during most of the period after RFR exposure than after sham-exposure and became comparable for the two treatments toward session end. The RFR-exposed rats were often seen sleeping during middle parts of sessions.

In the second part, rats were trained to repeatedly swim a 6-meter channel for 24 hours, and each rat's performance versus time was scored as its median swim speed for each successive block of 20 traverses. In one experiment, rats were sham-exposed or exposed at 6.3 W/kg for 30 minutes and tested immediately after treatment to determine any prompt effects. Their mean performance was similar to that of their sham group for about 200 traverses, but was below mean control speed for about the next 100 traverses, after which both groups again performed comparably. In two other similar experiments, the RFR level was 11 W/kg and the rats were tested immediately or after 1 day of delay. Measurements of colonic temperatures immediately after treatment showed that the rats had been rendered severely hyperthermic. The performance of the group tested right after exposure was clearly impaired by the hyperthermia, but the group tested 1 day later showed recovery and yielded results similar to those of the 6.3-W/kg group.

In the third part of the study, water-deprived rats were trained to press a lever in a complex vigilance-discrimination task to obtain small quantities of saccharin-flavored water. Then each rat was tested on five successive days. On the first day, all were sham-exposed. During the next four days, each group was exposed for one 30-minute period each at 6.5 and 11 W/kg and two of sham-exposure. Performance was tested for 30 minutes after each treatment. The mean error rate 5 minutes after exposure at 6.5 W/kg was significantly higher than after sham-exposure, but dropped to the the latter range at 15 and 25 minutes. After exposure at 11 W/kg, however, the mean error rates were all much higher than after sham-exposure. The mean number of responses diminished with increasing RFR level, but the decreases at higher levels were related to cessation of responding rather than lower licking rates, an effect most likely associated with warming.

Monahan and Ho (1976) exposed mice for 15 minutes within a waveguide to 2.45-GHz CW RFR at forward powers up to 4.8 W in an ambient temperature held at 24 ^{o}C by air flow through the waveguide. The mean SAR and the mean percentage of forward energy absorbed were measured at 5-minute intervals. In another experiment, the exposures were limited to 10 minutes and the absorptions were recorded at 12-second intervals. The mice could not be watched within the waveguide, but the results of both experiments showed that they had oriented themselves to reduce their percentages of RFR energy absorbed and SARs when the forward power was about 1.7 W (initial SAR 28 W/kg) or higher.

Lin et al. (1977) sham-exposed or exposed food-deprived rats to 918-MHz RFR at 10, 20, or 40 mW/cm^2 (2.1, 4.2, or 8.4 W/kg) during 30-minute sessions. The rat holder was a truncated cone of rods designed to allow the rat to poke its head through the narrower end and move it freely. A small upward head movement interrupted a horizontal light beam, thereby registering a count. The rat was required to do 30 such movements rapidly and regularly for a food pellet. A downward head movement gave access to the pellet delivered.

One of three rats was exposed for 30 minutes each at 2.1, 4.2, and 8.4 W/kg on consecutive days, another was exposed at the same levels on alternate days, and a third was given 30-minute sessions of sham-exposure. No significant effects on performance were seen at 2.1 or 4.2 W/kg. At 8.4 W/kg, the performance of the two RFR-exposed rats did not change during the first 5 minutes. However, both rats displayed heat stress and diminished performance (in different ways) during the remaining 25 minutes. Another rat was exposed at successively higher levels up to 32 mW/cm^2 (6.7 W/kg), at which it exhibited similar signs of heat stress. Its performance rates indicated a threshold between 30 and 40 mW/cm^2 (6.3 and 8.4 W/kg).

Schrot et. al. (1980) trained 3 rats to respond to auditory stimuli with four presses on three levers in a specific sequence that was changed for each session. Just before each session, the rats were either sham-exposed or exposed to pulsed 2.8-GHz RFR at one average power density in the range 0.25-10 mW/cm^2 (0.04-1.7 W/kg) for 30 minutes. Sessions were conducted daily, 5 days a week. Exposure at 10 mW/cm^2 (1.7 W/kg) of all three rats yielded higher error-responding rates, lower sequence-completion rates, and alterations in the normal acquisition pattern. Similar effects were seen at 5 mW/cm^2 (0.7 W/kg) but to a lesser extent. Below 5 mW/cm^2, most data points were within the control range, but a few were outside that range. The significance of the latter points is uncertain.

Gage and Guyer (1982) trained rats to perform on a reinforcement schedule in which the opportunity to obtain a food pellet was presented on the average of once each minute in a preplanned sequence of intervals without cueing. After training, groups were exposed to 2.45-GHz RFR for 15.5 hours at 8 or 14 mW/cm^2 (1.6 or 2.8 W/kg) and 22, 26, or 30 ^{o}C ambient temperature. The response rates at each ambient temperature diminished directly with increasing RFR level, but the effects of ambient temperature per se were not consistent.

Lebovitz (1981), sham-exposed and exposed groups of rats to 1.3-GHz pulsed RFR unrestrained in individual waveguides. In each waveguide were a vertical displacement bar (behavioral operandum), a means for illuminating the operandum as a cue, and a means for delivering food pellets. Before exposure, groups of food-deprived rats were trained to press the bar for food pellets until they learned to press the lever 5 successive times to obtain a pellet (a fixed-ratio-5, or FR-5 schedule). Those that performed at the highest and most stable rates were trained further to respond only when the operandum was illuminated (a multiple fixed-ratio, extinction schedule of reinforcement). During training, the FR schedule was gradually raised to FR-25. Their responses when the operandum was illuminated (SD) and when it was not illuminated (Sd, which yielded no pellets) were counted separately. Half the rats were assigned to the RFR group and half to the sham group. Exposures were for 3 hours daily, 5 days a week. Behavioral sessions were begun 15 minutes after exposure start and were halted 15 minutes before exposure end, with each behavioral session divided into 6 equal sequential blocks to evaluate intrasession changes.

The results for 8 weeks of exposure at 1.5 W/kg (3.9 mW/cm^2) showed no significant SD differences between the RFR and sham groups. Slight declines in rates during sessions were seen in both groups. The response rates for Sd were more variable than for SD. The intrasession declines in Sd rates, which were also evident for baseline and recovery weeks, was sharper than for SD, but there were no significant differences between the RFR and sham groups.

Groups exposed for 9 weeks at 3.6 W/kg (9.2 mW/cm^2) also showed no significant differences in SD response rates. There were marginally significant changes in weekly rates, and the intrasession decline in rate was significant. The Sd response rates again showed sharp intrasession declines for both groups. Results for 6 weeks of exposure at 6.7 W/kg (17.2 mW/cm^2) showed no significant differences between groups in overall SD response rates.

Based on the negative results for SD and Sd at 1.5 W/kg and the doubtfully significant decline in Sd rate at 3.6 W/kg, the author suggested that the latter RFR level could be the approximate threshold for modifying the rat behavioral paradigm studied. The author also indicated that 6.7 W/kg is the approximate resting metabolic rate for a rat, so that RFR level represents a doubling of the heat dissipation requirements of the rat. They therefore concluded that thermal factors were likely involved in the positive results.

Lebovitz (1983) exposed similarly trained groups of rats to CW or pulsed 1.3-GHz RFR and tabulated their SD and Sd response rates, called S+ and S- in this paper. The results for 3.6 W/kg and 5.9 W/kg were consonant with those of the previous study. Also, the S+ and S- rates for pulsed RFR at 6.7 W/kg (17.2 mW/cm^2) were similar to those with CW RFR at 5.9 W/kg (15.2 mW/cm^2). (Equipment limitations did not permit a closer match of SARs.) The author concluded that the differences in rates between the pulsed-RFR and sham groups were not ascribable to the pulsed character of the RFR per se. Core temperatures were measured in other rats. Exposures to CW or pulsed RFR at 3.5 W/kg, the approximate threshold above, yielded no significant differences in rectal-temperature changes compared with rats similarly sham-exposed. However, exposures at 6.3 W/kg yielded increases of 0.5-1 ^{o}C, with no

significant duration-dependent differences. Thus, the thermal basis for the behavioral changes above is evident.

D'Andrea et al. (1986a) exposed a group of 14 chamber-adapted rats to 2.45-GHz CW RFR at 0.5 mW/cm^2 (0.14 W/kg) 7 hours daily for 90 days. Body masses and intake of food and water were measured daily. Each rat was tested monthly for its threshold reactivity to footshock by observing its paw movements in response to electric shocks of varied intensity within a gridded-floor chamber. Differences in body mass, food and water intake, or threshold footshock reactivities relative to those of 14 sham-exposed rats were not significant. Right after such treatment, 7 rats of each group were assessed for open-field behavior, shuttlebox performance, and lever pressing for food pellets on an interresponse time schedule. The rest of the rats were examined for gross pathology, which showed no significant differences ascribable to the RFR. Major changes were seen in the open-field tests, but none of the differences were related to RFR exposure. Open-field tests done 60 days after treatment yielded similar results.

Shuttlebox performance was tested for responses to an electric shock given right after presentation of a tone and white light as a warning. The rat could prevent presentation of the shock by crossing to the other side of the shuttlebox during 10 seconds of the warning (an avoidance response), or could cross while receiving the shock (an escape response). The time lags (latencies) for avoidance and escape responses were recorded. The shuttlebox responses were highly variable: 4 of the RFR-exposed rats showed relatively long escape latencies and poor avoidance, whereas the other 3 RFR-exposed rats did as well as the 7 sham-exposed rats. Overall, the differences were not statistically significant. The shuttlebox test done 60 days after treatment also showed no significant differences in mean latencies or their variances.

Two days after the shuttlebox testing, the rats were deprived of food and trained daily to press a lever twice for a food pellet, with a specific time interval between the presses. The training was rendered progressively more difficult until the rats were required to do the second press only between 12 and 18 seconds after the first press to obtain a food pellet. During the training, the RFR group earned fewer pellets than the sham group, but the differences at corresponding times and overall were not significant.

The results of this study and of two similar studies in the same laboratory (D'Andrea et al., 1986b; DeWitt et al., 1987) were not fully consistent and showed little if any statistically significant differences between RFR-exposed and sham-exposed rats, but suggested that the threshold for behavioral responses to 2.45-GHz RFR in rats may be in the range 0.5-2.5 mW/cm^2 (0.14-0.70 W/kg).

Mitchell et al. (1988) exposed chamber-adapted rats to 2.45-GHz CW RFR at 10 mW/cm^2 for 7 hours within an anechoic chamber. Calorimetric measurements with rat carcasses yielded a spatial mean whole-body SAR of 2.7 W/kg. Right after treatment, each rat was tested for spontaneous locomotor activity, acoustic startle response, and retention of a shock-motivated passive avoidance task. Lower activity was seen in RFR-exposed rats than in sham-exposed rats. In the startle-response test, each rat was subjected to 20 intense acoustic pulses at variable intervals in the range 20-60 seconds, and

the response of the rat during each acoustic pulse was determined. The startle responses of RFR-exposed rats was significantly lower than for sham-exposed rats. Each rat was then placed in the lighted smaller part of a gated, two-chamber shuttle box, the larger part of which was dark and equipped to deliver an electric shock. The gate was opened after 1 minute, and if the rat moved into the larger chamber within 2 minutes, it was given a shock, but if it remained in the smaller chamber for more than 2 minutes, it was removed and not tested further. One week later, retention of the shock experience was tested in the box by allowing each rat 5 minutes (instead of 2 minutes) within the smaller chamber to react. The differences in passive avoidance activity between the RFR and sham groups were not significant.

Akyel et al. (1991) trained groups of 4 rats each on three different behavioral schedules to obtain food pellets. After training, each rat was exposed once a week for 10 minutes to 10-μs pulses of 1.25-GHz RFR at 1-MW peak forward power, with its long axis parallel to the electric component of the RFR. During sessions, the average forward power was held constant at 4, 12, 36, or 108 W, obtained by using a pulse repetition frequency of 240, 720, 2160, or 6480 pps. Each rat was administered all four RFR levels in a quasi-random weekly order. The whole-body specific absorptions (SAs) and whole-body specific absorption rates (SARs) respectively ranged from 0.5 to 14.0 kJ/kg and 0.84 to 23.0 W/kg. Testing of each rat was begun right after exposure end.

At the three lower RFR levels, no significant differences in any of the three behavior schedules were seen. At the highest level (14.0 kJ/kg, 23.0 W/kg), however, the rats that were trained on two of the schedules failed to reach baseline performance, and those on the third exhibited variable effects. Exposures at that level caused an average rise in colonic temperature of 2.5 ^{o}C, and the rats did not respond at all for about 13 minutes after exposure completion. The authors concluded that those behavioral changes were thermally induced.

Galloway (1975) trained rhesus monkeys to press one of three levers when that lever was lit in order to obtain a food pellet (discriminative behavior). After training, the head of each monkey was exposed with an applicator to 2.45-GHz RFR at estimated mean head SARs of 7, 13, 20, 27, and 33 W/kg, and the effects on their performance were examined. The RFR was administered for 2 minutes just before each behavioral session but was stopped earlier if the monkey began to convulse. Convulsions occurred for all exposures at 33 W/kg, and often at 20 W/kg. Each monkey was exposed at least twice at each level during a 9-month period. Also, three of them were exposed at 13 W/kg for 5 daily 1-hour schedules of 2 minutes on and 1 minute off, totaling 40 minutes of exposure per day. No effects on that discriminative task were evident for either exposure regimen.

In a repeated-acquisition test, the three levers were illuminated sequentially four times in a specific order, and each monkey had to press the levers in the correct sequence to obtain a pellet. Sessions of 60 trials were conducted daily before exposure, with the correct sequence changed each day. In the sessions just preceding RFR exposure, a slight learning trend (diminishing error rate) was seen, but the changes were too small to ascribe significance. This was also true for the results at all RFR levels except 33

W/kg, for which the error rate at session start was highest. Thus, except possibly for the latter result, the RFR had no effect on this behavioral paradigm.

Cunitz et al. (1975) inserted the head of a 3-kg or a 5-kg rhesus monkey through a hole in the bottom of a 383-MHz resonant cavity, with the monkey facing a diamond array consisting of the ends of four light pipes mounted through the cavity's side wall. Each monkey was trained in this apparatus to move a lever to the left, right, up, or down, when any of the pipes was lit, to indicate the position of that pipe end in the array. For criterion performance, the monkey had to do 100 correct lever presses to obtain a food pellet. During testing, the pipes were lit in random order. A correct response produced the lighting of another pipe plus a tone for 0.75 second. An incorrect response yielded a 3-second timeout during which all lights were off and lever movements had no consequences.

In each session, the monkey's head was exposed to 383-MHz RFR for 2 hours at one input to the cavity in the range 0-15.0 W. The head SARs were estimated to range up to 33 W/kg and 20 W/kg respectively for the 3-kg and 5-kg monkey. The larger monkey was also exposed at 17.5 W (23 W/kg). The monkey was restrained in a chair during the first hour, and the testing was done for the second hour. Sessions were conducted on 5 consecutive days at each level, with sham-exposure sessions before the RFR was raised to the next level. The lowest head SARs for diminished performance by the two monkeys were about the same: 22 and 23 W/kg.

Scholl and Allen (1979) trained three rhesus monkeys in a visual-tracking task that required each monkey to move a lever so as to hold a continuously moving spot within a prescribed clear area on the screen of a display monitor. The spot was moved electronically in a specific pattern, and the lever responses generated continuous difference signals (errors). The central 15% of the screen was clear and comprised the on-target area. The monkey received a brief electric shock for each 1 second accumulated outside the clear on-target area.

After training, the monkeys were exposed to horizontally polarized, 1.2-GHz CW RFR at 10 and 20 mW/cm^2 (measured at the center of the head in the absence of the monkey) for 2 hours each at one level and at the other level 2 days later. This polarization and frequency were chosen to provide half-wave resonant absorption in the monkey head. The corresponding head SARs were 0.8 and 1.6 W/kg. The data on mean tracking errors clearly showed that their performance was not diminished by RFR exposure.

De Lorge (1976) trained five rhesus monkeys to perform the following task while seated: Each monkey was required to press a lever in front of its right arm, thus producing either a low-frequency tone to signal that no food pellet will be coming, or a higher-frequency tone for which the monkey had to press a lever in front of its left arm to receive a pellet. During 1-hour training sessions, pellets were made available at variable intervals averaging about 30 seconds. During 2-hour training sessions, pellets were made available at intervals of about 60 seconds. The monkeys were exposed frontally to 2.45-GHz RFR at levels in the range 4-72 mW/cm^2 measured at head height. Estimated head SARs were 0.4-7.2 W/kg (0.1 W/kg per mW/cm^2).

After the monkeys achieved stable performance, they were tested on the variable 30-second delivery schedule in 1-hour sessions during which each was exposed to the RFR at 4 or 16 mW/cm^2 (0.4 or 1.6 W/kg head SAR) for 30 minutes. Their performances were not affected by either RFR level. Only three of them were tested on the variable 60-second delivery schedule in 2-hour sessions, during which they were exposed for 1 hour at levels in the range 16-72 mW/cm^2. One of them was also exposed at 16 mW/cm^2 during entire 2-hour test sessions. The performances of all three monkeys showed no significant departures from control rates for up to 52 mW/cm^2 (5.2 W/kg) and for two of them at 62 mW/cm^2 (6.2 W/kg); at that level, the performance of the third monkey was about 80% of its mean control rate. At 72 mW/cm^2 (7.2 W/kg), all three performed at about 50% of their mean control values. Those results suggested that the monkeys had reacted to body heating by the RFR at the higher levels, which diminished their performance.

De Lorge (1979) trained four squirrel monkeys to press either the right or the left lever on top of a chair to obtain a food pellet. At first, a red light and a blue light were turned on alternately with each successive press of the levers. Next, the contingencies were changed such that presses of the right lever continued to alternate the red and blue lights (without reward) but a press of the left lever was rewarded only when the blue light was on. Each of the next stages of training required a higher number of right-lever presses to turn on the blue light. The last stage was a schedule in which each right-lever press yielded either a half-second of red light or 10 seconds of blue light, with only a left-lever press during the latter yielding a pellet.

Each monkey was then exposed from above to 2.45-GHz RFR at levels in the range 10-75 mW/cm^2. SARs were estimated to have been 0.5 to 3.75 W/kg. In daily 1-hour sessions, the RFR exposures were done during the middle 30 minutes, with the other two 15-minute periods for obtaining baseline data. In daily 2-hour sessions, exposures were during the middle 1 hour. Neither duration caused any obvious physical changes in the monkeys. No consistent behavioral changes occurred below 50 mW/cm^2 (2.5 W/kg); above that level, the effects increased with RFR level. During the 1-hour sessions, only the rate of right-lever responses showed an RFR-induced change: a slight trend toward lower rates with increasing RFR level. The results for the 2-hour sessions (1-hour exposures) were similar, but more pronounced. The right-lever-response rate versus RFR level varied widely among the monkeys, but at 60 mW/cm^2 (3.0 W/kg), all showed decrements to about 60%.

The author concluded that the observed behavioral changes were temporary and clearly related to hyperthermia. Consistent changes were seen when rises in rectal temperature exceeded 1 ^{o}C, which corresponded to a threshold between 40 and 50 mW/cm^2 (2.0-2.5 W/kg). The author noted that similar results had been obtained with rhesus monkeys tested for the same behavioral task during exposure to 2.45-GHz RFR, but with a threshold 10 to 20 mW/cm^2 higher, and suggested that RFR-induced behavioral changes in different species may be scaled on the basis of body mass.

The findings of this study, reinforced by the similar results with rhesus monkeys, are important because the measurements of performance of a

complex behavioral task during exposure to RFR were carried out with two species much closer to human physiology and intelligence than more commonly used non-primate laboratory animals, and because reasonably accurate RFR thresholds for each primate species were determined.

De Lorge (1984) similarly trained rhesus monkeys to perform a task in which each monkey was to press a lever in front of its right hand (an observing response), which produced a brief low tone to signal that no food pellet will be delivered or a longer high tone to signal the availability of a pellet. If the monkey pressed a lever in front of its left hand while the high tone was on (a detection response), the tone would cease and a pellet would be delivered. A response on the left lever at other times produced a 5-second interval during which presses of the right lever yielded only the low tone.

After stable performance was attained, each monkey was frontally exposed, during 1-hour sessions, to vertically polarized 225-MHz CW RFR (near the whole-body resonant frequency), or to pulsed RFR at 1.3 GHz or 5.8 GHz (both above whole-body resonance). The exposures to 225 MHz were at 5-11 mW/cm^2 (2.0-4.4 W/kg); those to 1.3-GHz RFR were at 20-95 mW/cm^2 average (2.6-12.4 W/kg); and those to 5.8-GHz RFR were at 11-150 mW/cm^2 (0.34-4.7 W/kg). The results yielded average-power-density thresholds for behavioral effects that increased with frequency: 7.5 mW/cm^2 at 225 MHz, 63 mW/cm^2 at 1.3 GHz, and 140 mW/cm^2 at 5.8 GHz. However, the corresponding whole-body SARs varied up and down with frequency: respectively 3.0, 8.2, and 4.3 W/kg, presumable because of differences in penetration depth. The detection-response rate on the food lever was not consistently affected by RFR exposure at any frequency: No effect was observed for 225 MHz or 5.8 GHz; for 1.3 GHz, a decreased response rate was occasionally observed, but only at 83 mW/cm^2 (10.8 W/kg) or higher.

Exposure to 5.8-GHz RFR at 150 mW/cm^2 also produced minor burns on the faces of three of the monkeys, with the worst burns occurring between the eyes and along the orbitonasal area. The erythema disappeared within a few days except in one monkey who continually irritated the burned skin by removing scabious material. No burns occurred at 140 mW/cm^2 (4.4 W/kg), the behavioral threshold for this frequency, or at the highest levels of the other frequencies. The small penetration depth for 5.8 GHz (about 0.8 cm) probably was an important factor.

D'Andrea et al. (1989) trained five rhesus monkeys to operate three levers (left, right, center) in various sequences to obtain food pellets. The sessions were 60 minutes long. The task during each session comprised three successive 10-minute schedules of lever presses, followed by a repeat of the same three schedules.

In the first 10-minute schedule, the monkey was required to withhold responses for 8 seconds after the start of an audio tone, and then to respond only within the next 4 seconds; the correct response during those 4 seconds was two presses of the left lever within 2 seconds of each other. The authors called this an interresponse-time (IRT) schedule. The second 10-minute period involved a time-discrimination (TD) schedule in which a press of the center lever in the presence of blue light yielded white light of either short or

long duration in random fashion; at the end of either duration, the white light was replaced with red and green light. For the monkey to obtain a pellet when the red and green light was present, it had to press the right lever if the preceding white light was of short duration or the left lever if the preceding white light was of long duration.

During the third 10-minute period, a fixed-interval (FI) schedule was used: The monkey was presented with a continuous high tone, and its first press of the right lever after 55 seconds yielded a pellet.

During the 60-minute behavioral test sessions, each monkey was sham-exposed or exposed from above to 3-μs pulses of 1.3-GHz RFR at a root-mean-square pulse power density of 131.8 W/cm^2. The peak SAR was 15.0 W/kg in the head and 8.3 W/kg whole-body. The pulse repetition rate was 2, 4, 8, 16, or 32 pps, with corresponding average power densities of 0.92, 1.85, 3.70, 7.40, or 14.80 mW/cm^2.

The results showed no significant differences between sham- and RFR exposures in any of the behavioral responses. The authors noted that the the energy absorbed in the head by each pulse (280 mJ/kg) was well above the threshold for the RFR-auditory effect, and remarked that if such auditory stimulation did occur, it produced no obvious effect on the trained behavior.

In overall summary, many of the studies on avoidance behavior by animals indicate that RFR could be a noxious or unpleasant stimulus. There is much evidence, however, that changes in behavioral patterns induced by RFR are responses by their thermoregulatory systems, either to minimize absorption of heat in normal or warm ambient environments (including high levels of humidity) or to obtain warmth in relatively cold environments. Thus, other than possible auditory perception of RFR pulses, animals do not appear to directly sense RFR.

The results of studies on disruption of performance or learned behavior by RFR were variable; however, most of the findings showed that the behavioral changes were ascribable to the added thermal burden imposed by the RFR, and specifically were significant at measured or estimated whole-body SARs well in excess of 1 W/kg.

It is worth emphasizing that the behavioral findings of the primate studies are more relevant than those with the other animal species with regard to possible effects of RFR on human behavior, because the tasks the primates had to learn were far more complex, and because their physiologies and intelligence are much closer to those of humans. It is also noteworthy that reasonably accurate thresholds for RFR-induced behavioral changes were determined for each primate species studied, and that those thresholds served as a basis for the SCC 28 (1991) human-exposure standard.

3.7.2 RFR AND DRUGS

Various studies have been conducted on possible interactive effects of exposure to RFR and medications or other drugs taken or administered. Those discussed below are representative.

Thomas et al. (1979) trained four food-deprived rats on a fixed-interval, 1-minute (FI-1) schedule to press a bar for a pellet. After stable baseline patterns were achieved, an effect-versus-dose function for the psychoactive drug chlordiazepoxide (tradename *Librium*), given 30 minutes before a session, was established. This function showed that the responding rate rose with increased drug dose up to 10 mg/kg, attaining 2-3 times the baseline rate at that dose. At still higher doses, the responding rate decreased, attaining zero at 40 mg/kg.

After training, the rats were exposed to 2.45-GHz RFR at 1-W/cm^2 peak, 1-mW/cm^2 average (0.2 W/kg) during the 30 minutes before each bar-pressing session (starting right after drug injection). RFR exposure yielded the same shape of effect-versus-dose function, but the magnitudes were generally higher by a factor of about 2. By contrast, RFR exposure in the absence of any drug injection produced no difference in responding rate.

The results of this investigation are unequivocal, but the mechanisms are obscure. For example, although average power density and whole-body SAR were low, local SARs in brain regions that are target areas for central actions of chlordiazepoxide may have been high enough for a thermally potentiating effect. It is also conceivable that the pulse parameters produced the RFR-hearing effect during the 30-minute pre-session period. If so, however, not clear is whether or how any influence of this effect would have carried over into sessions during which RFR was absent.

Thomas and Maitland (1979) also trained six food-deprived rats to depress a lever on a schedule in which a second response at least 18 seconds after a first response was rewarded with a pellet, but a second response in less than that time interval reset the timing period. After such training, effects of exposure to the 2.45-GHz pulsed RFR (0.2 W/kg) used previously were sought on the dose-response function of the psychoactive drug d-amphetamine.

Three of the rats were dosed with the drug once per week and exposed for 30 minutes (single-exposure condition). Their behavior was observed for 1 hour right after exposure for any direct drug-RFR interaction. For detection of possible cumulative action of the RFR, the other three rats were dosed with d-amphetamine once a week and exposed for 4 days a week, 30 minutes daily (multiple-exposure condition), except on drug-injection days. On those days, their behavior was observed for 30 minutes after injection. The sessions were conducted for 13 weeks, and included sham-exposures and saline injections for all six rats.

For the three rats studied under the single-exposure condition, the mean response rates (in total responses per minute) after injection of saline and sham-exposure, and after injection of saline and RFR exposure, were comparable to baseline performances. When those rats were given d-amphetamine and sham-exposed, their mean response rates rose with drug dose to a maximum at 2.0 mg/kg, with consequent reductions in the frequency of correct responses that yielded reinforcement. At higher doses, the mean response rates dropped sharply, to zero for 4.5 mg/kg.

By contrast, the mean total response rate of those rats dosed with the drug and exposed to the RFR rose to values significantly higher than for the

corresponding doses with sham-exposure, with maximum at 0.5 mg/kg. Above 0.5 mg/kg, the mean total response rate declined sharply, to zero for 1.5 mg/kg. Those results show that RFR exposure after injection of a given dose of d-amphetamine yielded behavior similar to that obtained with a larger dose without RFR exposure.

For the three rats studied under the multiple-exposure condition, the mean baseline performance and mean performances for saline injection followed by sham- or RFR exposure did not differ significantly from the values for the other saline-injected rats. The dose-response functions of the rats with and without multiple RFR exposures were qualitatively similar to those with and without single RFR exposures even though the performances of the former group were determined 24 hours after the final exposure. With the multiple sham-exposures, maximum responses were obtained for 2.0 mg/kg, with a sharp decline to zero for 4.5 mg/kg. The maximum responses for the multiple RFR exposures were obtained with 0.5 mg/kg, and the responses declined sharply to zero for 2.0 mg/kg.

The authors remarked that the modest average power density (1 mW/cm^2) may have produced relatively high local SARs, particularly by resonant absorption in the head, which could have selectively heated the brain. In addition, head resonance could have yielded energy values above the threshold for the RFR-hearing effect. However, the authors discounted those possibilities because they would not account for the persistence of behavioral effects for 1 hour after the single exposures and for 25 hours after the last of the multiple exposures.

The effects of body restraint, which could synergize with low RFR levels and stressful events to produce considerable elevations of body temperature, were considered and discounted because restraint of the rats injected with saline and exposed to RFR yielded no significant deviations from the baseline values, and the dose-effect functions of unrestrained and restrained rats not exposed to RFR were the same.

Since d-amphetamine has been reported to heighten human perception with various senses, one could hypothesize that rats can perceive lower levels of RFR under the drug's influence than without the drug, and that such drug-induced perception would change their behavior. However, this hypothesis would not account for the 24-hour persistence of RFR influence seen in the multiple-exposure group.

Thomas et al. (1980) described similar research with the drugs diazepam and chlorpromazine. Diazepam (tradename *Valium*) has been widely prescribed as a tranquilizer and muscle relaxant. Chlorpromazine is used as a sedative and as an antiemetic.

Four food-deprived rats each of two strains were trained on a fixed-interval, 1-minute (FI-1) schedule of reinforcement. After training, the dose-effect functions for diazepam were determined in one strain and for chlorpromazine in the other strain. One dose was injected 30 minutes before each session and the doses were administered in mixed order, with at least three replications for each dose. Response rates and patterns were compared with their corresponding baseline performances.

Chlorpromazine lowered performance with increasing dose for all four rats administered that drug. The response rates stayed within baseline variability for doses up to about 1 mg/kg and declined for higher doses. For those given diazepam, the drug caused slight increases in response rate at doses up to about 2.5 mg/kg, with decline at higher doses.

Having determined dose-effect functions for the drugs, the authors exposed each rat for 30 minutes to 2.8-GHz pulsed RFR at 0.2 W/kg right after administering each drug, and tested the rats at exposure end. The RFR did not alter the effects of chlorpromazine or diazepam, in contrast with the results with chlordiazepoxide and d-amphetamine. Such differences in findings are difficult to reconcile.

Ashani et al. (1980) sought possible alterations of the hypothermic effects in rats of anticholinesterase drugs at ambient temperatures of 25-26 ^{o}C and 10 ^{o}C by 10-minute exposures to 2.8-GHz pulsed RFR (2-μs pulses at 500 pps) at 10 mW/cm^2 (about 2 W/kg), and the influence of antidotes for such drugs. The results were mixed, but because few people ingest anticholinesterase drugs or their antidotes, there appears to be no direct significance of such findings with regard to possible effects of RFR on human health.

Pappas et al. (1983) did three experiments to determine whether RFR alters seizures induced by a specific drug, and to study the effects of RFR on the efficacy of chlordiazepoxide for counteracting such seizures. In experiment 1, rats were sham-exposed or exposed for 30 minutes to 2.7-GHz pulsed RFR (2-μs pulses at 500 pps) at average power densities in the range 5-20 mW/cm^2 (0.75-2.25 W/kg). Before exposure, each rat was weighed, its rectal temperature was recorded, and it was injected with 1.0 ml/kg of saline. After exposure, temperatures were recorded again, the rats were given the seizure-inducing drug pentylenetetrazol (PTZ) at doses in the range 0-80 mg/kg in 1.0 ml/kg of saline, and their seizure activity was studied.

In experiment 2, each rat was injected with chlordiazepoxide (CDZ) at 2.0, 7.5, or 15.0 mg/kg before exposure. Exposures were for 30 minutes at 0, 5, 10, or 15 mW/cm^2 in factorial combination with the CDZ doses. After exposure, 70 mg/kg of PTZ was injected, and the strength of CDZ-inhibition of seizure-induction by PTZ was studied. The doses of CDZ and PTZ used were derived from unpublished results of a pilot study.

In both experiments, the rats were observed for signs of seizure activity for 8 minutes after injection of PTZ. The latency interval to the onset of the first sign was recorded, and seizure intensity was rated from 0 (no seizure, normal exploratory activity) to 4 (wild running and convulsions with 99% mortality).

In experiment 1, the latency-to-seizure times after PTZ injection decreased with increasing PTZ dose for all RFR levels. Analysis of variance with PTZ dose and RFR level as independent variables yielded a significant effect of dose and a slight but significant main effect of RFR. The rats exposed at 15 mW/cm^2 (2.25 W/kg) showed significantly shorter latencies than the sham-exposed rats. Mean seizure-intensity score versus PTZ dose rose

monotonically with dose, with no apparent effect of RFR level. The seizure-intensity score was significantly higher for 15 mW/cm^2 (2.25 W/kg) than for 5 mW/cm^2 (0.75 W/kg), but no values of the RFR groups differed significantly from those of the sham-exposed group. There was no significant interaction between PTZ dose and RFR level for either endpoint. The authors suggested that the decreases in seizure latency and increases in seizure intensity at 15 mW/cm^2 (2.25 W/kg) could have resulted from local brain hyperthermia rather than from alteration of PTZ effect on brain neuronal activity.

Analysis of variance of the seizure-onset latencies in experiment 2 showed a significant CDZ-dose-dependent latency-time increase, a main effect of RFR level, and a significant CDZ-RFR interaction. By Tukey's test, however, the RFR effect could be ascribed to two observations: Rats given 7.5 mg/kg of CDZ had longer latencies after exposure at 15 mW/cm^2 (2.25 W/kg) than at lower levels, and latencies of rats given 15 mg/kg were shorter after exposure at 5 mW/cm^2 (0.75 W/kg) than at 0, 10, or 15 mW/cm^2 (0, 1.5, or 2.25 W/kg). Analysis of the seizure-intensity scores indicated significant main effects of CDZ dose and RFR level, and a significant interaction between them. All CDZ doses except the smallest (2.0 mg/kg) decreases the seizure intensity significantly relative to saline controls at every RFR level. However, the RFR effect was accounted for by only one difference: The rats given 7.5 mg/kg of CDZ and exposed at 15 mW/cm^2 (2.25 W/kg) showed a significantly lower seizure intensity than the corresponding sham-exposed rats.

The authors noted that 7.5 mg/kg was close to the threshold dose for protection against seizure and they reasoned that RFR-exposure may be effective only near the dose threshold, since 15 mg/kg of CDZ already provided effective protection (without RFR) whereas 2.0 mg/kg offered virtually none. They also suggested the possibility that the apparent positive findings were ascribable to random (Type II) statistical error. Experiment 3 was done to test these hypotheses. In experiment 3, groups of rats were exposed for 30 minutes at 0, 5, 10, 15, or 20 mW/cm^2, after which they were given 60 mg/kg of PTZ; other groups were given 7.5 mg/kg of CDZ, exposed at those RFR levels, and then given 70 mg/kg of PTZ. In this experiment, the principal experimenter was unaware of the RFR level given each rat.

Analysis of variance of the core-temperature data for rats injected only with PTZ showed a significant effect of RFR level; by Tukey's test, temperature rises of RFR-exposed rats relative to those of sham-exposed rats were significant at 10 mW/cm^2 (1.5 W/kg) or higher. However, there was no significant relationship between RFR level and latency-to-seizure time or seizure-severity score. For rats given CDZ before RFR-exposure, analysis of variance of the temperature data again showed a significant effect of RFR level, but Tukey's test showed that the mean temperature of only those exposed at 20 mW/cm^2 (3 W/kg) significantly differed from that of the sham-exposed rats.

Comparison of the temperature-vs-power-density curves of CDZ/PTZ rats and PTZ-only rats indicated that the hyperthermic effects of RFR-exposure were attenuated by CDZ and/or that the hypothermic effects of CDZ were counteracted by RFR-exposure. However, analysis of variance of the seizure data for the CDZ/PTZ rats showed no significant effect of RFR level on latency or severity.

Thus, despite the thermal antagonism between CDZ and RFR, the latter did not alter the protective efficacy of this CDZ dose against PTZ-induced seizure.

The authors remarked that the results of experiment 3, in which a more rigorous rater-blind scoring procedure was used, did not support the earlier findings that 15 mW/cm^2 (2.25 W/kg) or even 20 mW/cm^2 (3 W/kg) enhanced PTZ seizures and increased the antiseizure protection of CDZ at 7.5 mg/kg. They regarded the few apparently positive results as spurious, Type II errors, but they did not rule out the possibility of experimenter bias.

The authors also noted that their negative results seem to be at variance with those of Thomas et al. (1979), who found that exposure of rats trained on a fixed-interval (FI) behavior schedule to pulsed 2.45-GHz RFR at 1 mW/cm^2 (average) did not alter their behavior. Thomas et al. (1979) also had established a dose-effect relationship for CDZ over the range 1-40 mg/kg on the FI behavior schedule. They then found that RFR-exposure immediately after administering CDZ yielded a dose-effect curve of the same shape as that without the RFR but of about twice the magnitude. Possible reasons for the differences in findings of the two studies (besides the widely different endpoints) would be speculative.

Lai et al. (1983) exposed unrestrained rats to pulsed, circularly-polarized 2.45-GHz RFR (2-μs pulses, 500 pps) in cylindrical waveguides (Guy et al., 1979) for 45 minutes at a spatially-averaged power density of 1 mW/cm^2 and ambient temperature of 22.0 ^{o}C. By calorimetry, the whole-body SAR was 0.6 W/kg. The authors noted that at this SAR, the range of average power densities for linearly polarized RFR would be 3-6 mW/cm^2. Control rats were sham-exposed. One of several drugs was administered right after exposure and its effects were studied.

The first experiment was directed toward determining the effect of RFR exposure on stereotypy induced by subcutaneous apomorphine injection. The stereotypic behavior of each rat was observed for 5 minutes right after injection and at subsequent 15-minute intervals for 1 hour. The rating scale below was used, with the sum of the five ratings taken as the score for the rat:

Rating 1: awake but largely immobile.
Rating 2: moving with short bursts of sniffing.
Rating 3: moving over the area of the cage with continuous sniffing and rearing.
Rating 4: some or no movement and continuous sniffing with head directed down.
Rating 5: same as 4, but with licking, biting, or gnawing.

The results of the first experiment yielded a mean score of 17.2 for 15 RFR-exposed rats and 14.5 for 9 sham-exposed rats (no variances given). The percentage of the mean score in each rating was displayed for each group. The RFR group yielded significantly lower percentages for ratings 1 and 3 and significantly higher percentages for ratings 4 and 5 than the sham group. The authors stated: "Microwave exposure shifted the distribution towards the higher scores, ie, more intense stereotypy with biting and clawing being observed in the microwave-treated animals."

In the next experiment, the effect of RFR on apomorphine-induced hypothermia was studied. Colonic temperatures were measured for 15 RFR-exposed and 12 sham-exposed rats right after exposure, then the rats were injected with apomorphine and their colonic temperatures were recorded again for 1 hour at 15-minute intervals. Results were shown as mean change in colonic temperature versus time interval after injection. Mean colonic temperature right after exposure was 38.3 ^{o}C for the RFR group and 38.2 ^{o}C for the sham group. Fifteen minutes after drug injection, the RFR group's mean temperature had decreased by 0.95 ^{o}C, whereas the decrease was only 0.63 ^{o}C for the sham group. By nonparametric test, the difference was significant, indicating that the hypothermic effect of apomorphine was enhanced by the RFR. Progressive recovery from the hypothermia at 30 and 45 minutes was evident for both groups.

Next, the effect of RFR on stereotypy induced by d-amphetamine was studied. Each rat was injected with d-amphetamine right after exposure and was watched for the presence of any of three normal behaviors (immobility, rearing, and forward walking) and three abnormal behaviors (backward walking, circling, and head swaying). They were observed for 1 minute every 5 minutes for 1 hour, starting 4 minutes after injection. Each behavior was recorded on an all-or-none basis and the total incidence of each was determined for each rat. The difference in average score for each of the six behaviors between the RFR-exposed and sham-exposed groups was nonsignificant.

The effect of RFR on amphetamine-induced hyperthermia was studied also. Colonic temperatures of rats were measured right after exposure and at 15-minute intervals during the 90-minute period after injection with d-amphetamine. Results were shown as the mean colonic temperature change for each group versus time interval after injection. The mean temperature at zero time was 38.3 ^{o}C for the RFR group and 38.2 ^{o}C for the sham group. The mean temperature of the sham group reached its maximum at 45 minutes, at which time it was 1.4 ^{o}C higher, and then it diminished to about 39.3 ^{o}C at the end of the 90-minute period. By contrast, the RFR group's temperature reached its maximum at 60 minutes, an increase of 1.2 ^{o}C, and diminished to 39.2 ^{o}C at 90 minutes. These differences in time-dependent temperature increases were significant.

In the final experiment, morphine was injected into rats at doses of 1, 5, 10, 15, or 20 mg/kg immediately after exposure. The number of rats that exhibited catalepsy (general muscular rigidity and a certain posture for more than 1 minute) 30 minutes after injection was recorded. Also recorded was the number of rats that died within 2 hours after injection.

The paper showed the percentages of RFR-exposed and sham-exposed rats that exhibited catalepsy for each dose, and the authors indicated that by chi-square test, the differences were significant. However, in an erratum (Lai et al., 1985), they indicated that the statistical method used was inappropriate and that use of the "logistic regression" method showed a positive dose-response in the sham group but no dose-response in the RFR group. Therefore, the responses of the sham group at low morphine doses were lower than of the RFR group and were higher at high doses.

The original paper indicated that no deaths had occurred in the RFR or sham group at 1 or 5 mg/kg, but that the differences in percentages of deaths at 10, 15, and 20 mg/kg were significantly higher in the RFR group. In the erratum, however, the authors stated: "The probability of death caused by morphine administration increased with dose in a similar way for both microwave- and sham-irradiated groups, with no significant effects of microwaves."

It is interesting to note that the mean colonic temperatures of the apomorphine-injected and amphetamine-injected groups immediately after exposure to RFR were both 0.1 ^{o}C higher than for their respective sham-exposed groups (38.3 versus 38.2 ^{o}C in both cases). Presumably the temperatures of the RFR group were even higher during exposure, and the postexposure difference between the RFR and sham groups was due to the residual thermal response to the RFR. In the light of this point, not clear was the influence of thermoregulation on the results. For both drugs, the differences in mean colonic temperature between RFR and sham groups during the postinjection intervals were smaller than the changes per se. With apomorphine, for example, the sum of the RFR group's mean pre-injection colonic temperature and its maximum change (15 minutes post-injection) was 37.35 ^{o}C, and the corresponding sum for the sham group was 37.57 ^{o}C, a difference of only 0.22 ^{o}C. Was this difference significant? Would similar results be obtained if pre-injection colonic temperatures were raised by an agent other than RFR?

The peak power density of the RFR pulses was at least 1 W/cm^2, within the range of perception of the pulses as sound. Thus, it is also possible that the rats perceived the pulses and were influenced thereby, but as noted above with respect to Thomas et al. (1979), whether the influence persisted into the postexposure period is unknown. Lacking in this investigation were data on control animals given saline instead of the drugs. Such data might have more clearly delineated subtle non-RFR factors that may have influenced the results.

In a similar study, Lai et al. (1984a) examined the effects of the same RFR on the actions of pentobarbital in the rat. In the first of two series, 13 unanesthetized, unrestrained rats were exposed to the RFR. Each rat's colonic temperature was taken right after exposure, after which the rat was injected with sodium pentobarbital at a dose sufficient to induce surgical anesthesia. After the rat lost its righting reflex, its colonic temperature was recorded at 15-minute intervals for 150 minutes, and the time interval after injection to regain the righting reflex was recorded. Another group of 13 rats was sham-exposed and similarly treated.

In the second series, baseline colonic temperatures were measured and the rats were injected with pentobarbital. After 15 minutes, by which time all of the rats had lost their righting reflex, 12 rats were exposed to the RFR for 45 minutes anteriorly (head toward source) and 10 rats posteriorly (rear toward source). Their colonic temperatures were recorded for 90 minutes after exposure as were their time intervals for regaining the righting reflex.

A nonparametric statistical method was used to compare the colonic-temperature-response curves, in which the temperature-response curve of each rat was approximated by orthogonal polynomials and the zero-order orthogonal

coefficients for the different treatment groups were compared by chi-square analysis. Student's two-tailed t-test was used to compare the colonic temperatures at corresponding times and to compare the time intervals for regaining the righting reflex.

The (conscious) rats in the first series did not show any preferred orientation during RFR exposure and there was no significant difference in mean colonic temperature between the RFR and sham groups immediately after exposure (37.8 ^{o}C for both). Mean colonic-temperature changes for each group versus time after pentobarbital injection indicated that both groups reached maximal hypothermia (about -3 ^{o}C) at 75 minutes. The mean temperature depressions at corresponding times were larger for the sham group than for RFR group until 90 minutes after injection; at 90 minutes, the two plots intersected, but none of the differences between the groups up to 105 minutes was significant. At corresponding times from 105 to 150 minutes, the mean depressions for the RFR group were significantly larger than for the sham group, i.e., recovery of the RFR group from the hypothermia was slower. Also, the mean time to righting-reflex recovery for the RFR group was significantly longer than for the sham group (100 versus 90 minutes).

In the second series, the baseline mean colonic temperatures of the injected rats before RFR- or sham exposure were 37.9 ^{o}C. For the groups sham-exposed in the two orientations, there was no significant difference in mean temperatures immediately after sham-exposure so their results were pooled. The mean colonic temperatures of the RFR groups right after anterior-exposure and posterior-exposure were respectively 34.6 and 34.7 ^{o}C, and for the combined sham group was 34.1 ^{o}C. The difference between the two RFR groups was not significant, but both values were significantly higher than for the sham group.

Plots of mean colonic-temperature change (from the values preceding injection) versus time after exposure showed that all three groups attained maximal hypothermia 30 minutes after exposure (45 minutes after injection). The mean changes at that time for the posterior-RFR, anterior-RFR, and sham groups were respectively about -3.8, -4.2, and -4.5 ^{o}C, but only the difference between the posterior-RFR and sham groups was significant.

From 30 to 90 minutes, all three groups showed recovery toward baseline temperatures, with no significant differences at corresponding times between anterior-RFR and sham groups. However, the temperatures of the posterior-RFR group were significantly higher than those of the other groups at corresponding times during that interval, indicating that the posterior-RFR group recovered from the hypothermia earlier. Moreover, those rats recovered their righting reflex more quickly (26, 45, and 50 minutes respectively for posterior-RFR, anterior-RFR, and sham groups, with the difference between the latter two groups not significant).

About the second series, the authors noted that the RFR diminished pentobarbital-induced colonic-temperature decreases and ascribed the effect to the energy absorbed. From their results that the RFR altered the core temperature of anesthetized but not of conscious rats, they suggested the functioning of a compensatory thermoregulatory mechanism during RFR exposure to maintain a constant core temperature, and that a similar effect has been

reported in animals after treatments with other drugs that disturb thermoregulation.

Another finding commented on by the authors was the smaller maximal colonic-temperature depression and earlier righting-reflex recovery time for the posterior-RFR group than the anterior-RFR and sham groups. They surmised that the orientation-dependent findings were due to differences in local energy depositions for the two orientations, which could yield differences in drug metabolism or kinetics.

Again, the pulse power density was within the range of perception of the pulses as apparent sound. It is thus possible that the conscious rats in experiment 1 perceived the pulses, but it would be difficult to connect such perception with the reported differences in pentobarbital-induced hypothermia and analepsis therefrom.

Lai et al. (1984b) also did experiments to determined the effects of the same RFR on ethanol-induced hypothermia and ethanol consumption. For the ethanol-hypothermia experiment, 15 rats were RFR exposed and 14 were sham-exposed for 45 minutes. Immediately after exposure, each rat was removed from its waveguide, its colonic temperature was measured, and it was injected with a solution of ethanol (3 g per kg of body weight in 25% of water by volume). The rats were then housed six to a cage and their colonic temperatures were measured with a thermistor inserted and removed at 15-minute intervals for 120 minutes.

Mean colonic temperatures of the RFR-exposed and sham-exposed rats right after exposure were respectively 38.2 and 38.3 ^{o}C, a nonsignificant difference. Ataxia developed within 5 minutes of ethanol injection, but righting reflex remained intact. The mean temperature changes versus time after ethanol injection for the two groups showed that hypothermia had occurred in the RFR group at a slower rate than in the sham group. For example, the temperature depressions 15 minutes after injection were about 0.4 and 0.9 ^{o}C for the RFR and sham groups, respectively, a significant difference; at 60 minutes, the corresponding depressions were about 1.5 and 1.8 ^{o}C, a significant difference also; at 90 minutes, the depressions were 1.9 ^{o}C for both groups and did not differ significantly at later times.

In the ethanol-consumption study, rats were given 90-minute sessions in the waveguides daily for 9 days. Drinking water was removed from the home cages 24 hours before the first session. On session days 1, 2, and 3, the rats were inserted in the waveguides for 45 minutes with the RFR source on "standby". At this time, a bottle containing a 10% sucrose solution was inserted in each waveguide and the amount consumed during the remaining 45 minutes was measured. The procedure on day 4 was the same except that half the rats (24) were selected randomly and exposed to the RFR, and the other half were sham-exposed for the full 90 minutes. On days 5-7, the procedure was the same as on days 1-3 except that a 15% ethanol + 10% sucrose solution was used, to render the ethanol more palatable.

On day 8, half the rats (group I, randomly selected) were exposed to RFR and the remaining rats (group II) were sham-exposed for 90 minutes, and the amounts of sucrose-ethanol solution consumed during that period were measured.

On day 9, the group roles were reversed: group I was sham-exposed, group II was RFR exposed, and fluid consumption was noted.

For days 1, 2, and 3 (during which all 48 rats were sham-exposed and offered the sucrose solution), the mean sucrose consumption successively rose significantly. On day 4, however, (when half were RFR exposed and the others sham-exposed for 90 minutes), the mean sucrose consumptions for the two groups did not differ significantly from each other or from the day-3 value.

For days 5, 6, and 7 (when all 48 rats were sham-exposed and offered the sucrose-ethanol solution), the mean sucrose-ethanol consumption varied up and down with time. For day 8 (when group I was RFR exposed and group II was sham-exposed), sucrose-ethanol consumption by group II did not change significantly but that of group I significantly increased. For day 9 (when group II was RFR exposed and group I was sham-exposed), consumption by group II significantly increased. Thus, RFR exposure had no apparent effect on sucrose consumption, but increases in sucrose-ethanol consumption were linked to RFR exposure.

Hjeresen et al. (1988) also studied the effects of RFR on ethanol-induced hypothermia in rats, but with 2.45-GHz CW instead of pulsed RFR (to avoid the RFR-hearing effect) and at 0.3 W/kg, half the SAR used by Lai et al. (1984b). On the day preceding each experiment, they weighed the rats, measured their colonic temperatures, and used the values to divide the rats into equivalent RFR and sham groups.

In the first experiment, four groups of six rats each were treated. One group was exposed to the RFR for 45 minutes; the colonic temperature of each rat was measured; the rat was injected i.p. with ethanol at 3.6 g/kg, 20% v/v, equivalent to the 3.0 g/kg, 20% v/v dose used by Lai et al. (1984b); and its temperature was measured again at 20-minute intervals for 2 hr after injection. The second group was sham exposed for 45 minutes and otherwise similarly treated. The third and fourth groups were RFR- and sham exposed, respectively, but were injected with saline instead of ethanol. The protocol was conducted on 8 successive days to assess for differences in rates of development of tolerance to ethanol-induced hypothermia. On the ninth day, all four groups were given ethanol and were RFR- or sham exposed as on the previous 8 days, to determine the levels of ethanol tolerance achieved and to assess the effects thereon of the RFR-exposures on days 1-8.

The mean colonic temperatures (and SEs) of the four groups at each measurement time were shown graphically for days 1, 3, 6, and 8. The temperatures just before and after the RFR- or sham exposure (preceding ethanol or saline injection) showed significant rises for each group on each day. On day 1, the temperature rises were all about 0.7 ^{o}C (to about 38 ^{o}C), with nonsignificant differences among the four groups. On day 3, however, the temperature rises differed considerably among the four groups, ranging from 0.5 ^{o}C for the RFR + ethanol group to 1.5 ^{o}C (almost to 39 ^{o}C) for the RFR + saline group. All of the rises were about 1.2 ^{o}C on day 6 and 1 ^{o}C on day 8, with no significant differences among the groups on either day. The authors ascribed these preinjection rises to rat stress due to handling, the colonic-temperature measurements, and the novelty of experimental situation, but did

not discuss how such large rises and the differences thereof among the groups on day 3 would affect the validity of their post-injection findings.

On day 1, the colonic-temperature measurements at 20-minute intervals after injection showed rapid drops for the two ethanol groups (RFR and sham) of about 3 °C (to about 35 °C) at 60 minutes. During the rest of the 2-hour period, the temperature of the RFR + ethanol group increased slowly (to 35.8 °C at 120 minutes), but that of the sham + ethanol group decreased further (to 34.6 °C at 80 minutes) and rose slowly (to 34.8 °C at 120 minutes); the differences between those two groups at 80, 100, and 120 minutes were significant. For the two saline groups on day 1, the mean temperature of the RFR group decreased slightly but nonmonotonically (by 0.2 °C at 120 minutes) and that of the sham group decreased monotonically (by 0.8 °C at 120 minutes), so the differences at corresponding times in the second half of the 2-hour period were significant.

Overall, the results for the four days showed that the hypothermia of the sham + ethanol group was less pronounced on each successive day, indicating the development of some ethanol tolerance (in the absence of RFR). The corresponding results of the RFR + ethanol group showed that the RFR did diminish the hypothermia on each day, but with the largest effect (differences between the groups) on day 6. The authors remarked that the RFR did not affect the rate of ethanol-tolerance development. Also evident in the graphs for day 6 were relatively large SEs for the sham + ethanol group (about ± 0.4 °C) in the second half of the 2-hour period, indicating that unknown factors may have contributed to the results of this control group during that day.

On day 9, when all four groups were administered ethanol after RFR- or sham exposure, the post-exposure temperature rises preceding ethanol injection were essentially the same for all four groups (about 1 °C). After ethanol injection, all four groups exhibited hypothermia, with the magnitudes of the effect in decreasing order by group as follows: sham + saline, RFR + saline, sham + ethanol, and RFR + ethanol. Comparisons of the results on day 9 for the sham and RFR groups given saline on days 1-8 indicate that the RFR on days 1-8 moderated the hypothermia induced by ethanol on day 9. The finding for the sham and RFR groups injected with ethanol on days 1-8 was similar. The smaller hypothermic effects in the latter two groups were ascribed to higher ethanol-tolerance development than in the former two groups.

In the next experiment, the duration of RFR exposure necessary to obtain RFR moderation of ethanol-induced hypothermia was assessed. One of two groups (8 rats each) was RFR-exposed and the other was sham exposed for 5 minutes, and both were injected with ethanol right after post-exposure colonic-temperature measurements. Two other groups were respectively RFR- and sham exposed for 15 minutes and injected with ethanol 15 minutes after exposure. Still other pairs of groups were exposed for 30 minutes and injected with ethanol 30 minutes after exposure, and exposed for 60 minutes and injected 60 minutes after exposure, respectively. As before, post-injection temperatures were measured at 20-minute intervals for 2 hours.

All eight groups exhibited deep hypothermia (to roughly 35 °C). The colonic-temperature differences between paired RFR and sham groups at corresponding times were nonsignificant, except for the pair treated for 60

minutes. For the latter pair, the temperatures of the RFR group from 40 to 120 minutes were significantly higher than the corresponding values of the sham group. However, unlike the other 7 groups (and those in the first experiment), the 60-minute RFR group exhibited only a small post-exposure pre-injection temperature rise, about 0.2 ^{o}C, compared with about 0.8 ^{o}C for its sham group, and larger increases for the 15-minute and 30-minute pairs.

The third experiment was directed toward determining the duration of RFR-induced hypothermia moderation. Five pairs of groups were RFR- and sham exposed for 45 minutes and each pair was injected with ethanol, one pair immediately after measurement of post-exposure temperature and the other pairs at 30, 60, 120, and 480 minutes after exposure. As before, the temperatures were measured at 20-minute intervals after injection. Maximum hypothermia moderation was seen for the RFR group injected right after measurement of post-exposure temperature. Successively less moderation was seen in the groups injected at the later intervals, with significant differences between paired groups only for delays of 30 and 60 minutes.

In the final experiment, the dependence of RFR-ethanol hypothermia interaction on ethanol dose was assessed. Four groups each were RFR- and sham exposed for 45 minutes, after which three pairs of RFR and sham groups were respectively injected with ethanol at 0.9, 1.8, or 2.7 g/kg and the fourth pair with saline. Again, temperatures were measured at 20-minute intervals after injection. Results were shown separately for the four RFR groups and the four sham groups; also displayed were the day-1 results for the RFR and sham groups administered 3.6 g/kg in the first experiment. The 5 sham groups showed successively deeper hypothermia with increasing ethanol dose as did the 5 RFR groups, and for each ethanol dose, the hypothermia of the RFR group was less deep than for the sham group.

It is noteworthy that the rises in post-exposure temperature (pre-injection) of the five RFR groups were comparable to one another, but the mean baseline (pre-exposure) temperature of the 3.6-g/kg RFR group was about 37.1 ^{o}C as compared with about 37.7 ^{o}C for the four RFR groups in the present experiment. A similar but smaller difference was obtained between the 3.6-g/kg sham group and the four sham groups in the present experiment. Also noteworthy was an apparent discrepancy between the sham-saline groups in the first experiment and the last experiment. In the last experiment, the mean temperature of the sham-saline group before exposure (baseline) was about 37.8 ^{o}C; it rose to about 38.8 ^{o}C during sham exposure; it then dropped to 38.0 ^{o}C 40 minutes post-treatment and stayed at that level for the remainder of the 2-hour period. By contrast, the mean baseline temperature for the sham-saline group in the first experiment was about 37.2 ^{o}C, the temperature rose during sham exposure to about 38.2 ^{o}C and gradually decreased monotonically to about 37.4 ^{o}C at 120 minutes. Such differences in results for control groups, as well as the previously discussed significant rises in colonic temperature during both RFR- and sham exposure, indicate the presence of large uncontrolled factors and render questionable most of the findings of this study.

Lai et al. (1992) exposed rats to the same pulsed RFR (2-μs pulses of 2.45-GHz RFR at 500 pps) at a whole-body SAR of 0.6 W/kg either once for 45 minutes or for 10 daily 45-minute sessions to determine the effects of the RFR

on the concentration and affinity of benzodiazepine receptors in the cerebral cortex, hippocampus, and cerebellum. The results of the single exposures indicated a significant increase of receptor concentration in the cerebral cortex but not in the hippocampus or cerebellum. There were no significant changes in the binding affinity of the receptors in any of the three regions. The results for the multiple exposures showed no change in receptor concentration right after the last exposure, a possible indication of adaptation to repeated exposures.

In a separate experiment, rats were placed in the waveguides with food and water 24 hours before exposure, to adapt them to the experimental situation. Immediately after a single 45-minute RFR- or sham exposure, the cerebral cortex was assayed for benzodiazepine receptors. The mean receptor concentration for the RFR-exposed rats was significantly higher than for the sham-exposed rats. Those results led the authors to suggest that because benzodiazepine receptors are responsive to anxiety and stress, low-level RFR can be a source of stress.

3.7.2.1 SUMMARY

Various studies have been conducted on possible interactive effects of exposure to RFR and medications or other drugs taken or administered. Those discussed below are representative.

Thomas et al. (1979) trained rats on a fixed-interval, 1-minute (FI-1) schedule to press a bar for a pellet. After stable baseline patterns were achieved, an effect-versus-dose function for the psychoactive drug chlordiazepoxide (tradename *Librium*), given 30 minutes before a session, was established. This function showed that the responding rate rose with increased drug dose up to 10 mg per kg of body weight, attaining 2-3 times the baseline rate at that dose. At still higher doses, the responding rate decreased; it attained zero at 40 mg/kg.

After training, the rats were exposed to 2.45-GHz RFR at 1-W/cm^2 peak, 1-mW/cm^2 average (0.2 W/kg) during the 30 minutes before each bar-pressing session. RFR exposure yielded the same shape of effect-versus-dose function, but the magnitudes were generally higher by a factor of about 2. By contrast, RFR exposure in the absence of any drug injection produced no difference in responding rate. The results of this study are unequivocal, but the mechanisms are obscure. For example, although the average power density and whole-body SAR were low, local SARs in brain regions that are target areas for central actions of chlordiazepoxide may have been high enough for a thermally potentiating effect. It is also conceivable that the pulse parameters produced the RFR-hearing effect during the 30-minute exposure preceding the bar-pressing session. If so, it is not clear whether or how this effect would have influenced the testing sessions themselves, during which the RFR was absent.

Thomas and Maitland (1979) trained six rats to depress a lever on a schedule in which a second response at least 18 seconds after a first response was rewarded with a pellet, but a second response in less than that time interval reset the timing period. After such training, effects of exposure to

the pulsed RFR (0.2 W/kg) used in the previous study were sought on the dose-versus-response function of the psychoactive drug d-amphetamine.

Three of the rats were dosed with the drug once per week and exposed for 30 minutes (single-exposure condition). Their behavior was observed for 1 hour right after exposure for any direct drug-RFR interaction. For detection of possible cumulative action of the RFR, the other three rats were dosed with d-amphetamine once a week and exposed for 4 days a week, 30 minutes daily (multiple-exposure condition), except on drug-injection days. On the latter days, their behavior was observed for the 30 minutes after injection. The sessions were conducted for 13 weeks, and included sham-exposures and saline injections for all six rats.

For the single-exposure condition, the mean response rates after saline injection and sham-exposure and after saline injection and RFR exposure were comparable to baseline performances. When those rats were given d-amphetamine and sham-exposed, their mean response rates rose with drug dose to a maximum at 2.0 mg/kg, with consequent reductions in the frequency of correct responses that yielded reinforcement. At higher drug doses, the mean response rates dropped sharply, to zero for 4.5 mg/kg. By contrast, the mean response rate of drug-injected rats and exposed to the RFR rose to values significantly higher than for the corresponding drug doses and sham-exposure, with maximum response rate at 0.5 mg/kg. Above 0.5 mg/kg, the mean response rate declined sharply, to zero for 1.5 mg/kg. Those results show that exposure to the RFR after injection of a given dose of d-amphetamine yielded behavior similar to that obtained with a larger dose without the RFR exposure.

The dose-response functions of the rats with and without multiple RFR exposures were qualitatively similar to those with and without single RFR exposures. With the multiple sham-exposures, maximum responses were obtained for 2.0 mg/kg, with a sharp decline to zero for 4.5 mg/kg. The maximum responses for the multiple RFR exposures were obtained with 0.5 mg/kg, and the responses declined sharply to zero for 2.0 mg/kg.

Thomas et al. (1980) did similar research with the drugs diazepam and chlorpromazine. Diazepam (tradename *Valium*) has been widely prescribed as a tranquilizer and muscle relaxant. Chlorpromazine is a sedative and an antiemetic. Four rats each of two different strains were trained on a fixed-interval, 1-minute (FI-1) schedule of reinforcement. After training, the dose-effect functions for diazepam were determined in one strain and for chlorpromazine in the other strain. One dose was injected 30 minutes before each session, and the response rates of the rats were compared with their baseline performances. Chlorpromazine lowered the performance of all four rats for doses above about 1 mg/kg. For the rats given diazepam, the drug caused slight increases in response rate at up to about 2.5 mg/kg and declines at higher doses.

After determining dose-effect functions for the drugs, the authors exposed each rat for 30 minutes to 2.8-GHz pulsed RFR at 0.2 W/kg right after administering each drug, and tested the rats at exposure end. The RFR did not alter the effects of either chlorpromazine or diazepam, in contrast with the results with chlordiazepoxide and d-amphetamine. Such differences in findings are difficult to reconcile.

Ashani et al. (1980) sought possible alterations of the hypothermic effects of anticholinesterase drugs in rats and the influence of antidotes for such drugs. Mixed results were obtained for 10-minute exposures to 2.8-GHz RFR at 10 mW/cm^2 (about 2 W/kg). Since few people ingest such drugs or their antidotes, there appears to be no direct significance of the findings with regard to possible effects of RFR on human health.

Pappas et al. (1983) did experiments to determine whether RFR alters seizures induced by the drug pentylenetetrazol (PTZ), and to study the effects of RFR on the efficacy of chlordiazepoxide (CDZ) for counteracting such seizures. In one experiment, rats were exposed for 30 minutes to 2.7-GHz pulsed RFR (2-μs pulses at 500 pps) at average power densities up to 20 mW/cm^2 (2.25 W/kg). After exposure, the rats were given PTZ at doses up to 80 mg/kg, and their seizure activity was studied. In another experiment, each rat was injected with anti-seizure CDZ at doses up to 15.0 mg/kg before exposure. After exposure, 70 mg/kg of PTZ was injected, and the degree of inhibition of PTZ-induced seizures by the CDZ was studied.

In both experiments, the rats were observed for signs of seizure activity for 8 minutes after injection of PTZ. The latency interval to the onset of the first sign was recorded, and seizure intensity was rated from 0 (no seizure, normal exploratory activity) to 4 (wild running and convulsions with 99% mortality).

In the first experiment, the latency times to seizure following PTZ injection decreased with increasing PTZ dose for all RFR levels. The rats exposed at 15 mW/cm^2 (2.25 W/kg) exhibited significantly shorter latencies than the sham-exposed rats. The mean score of seizure intensity increased with PTZ dose, with no apparent effect of RFR level. The mean score was significantly higher for 15 mW/cm^2 (2.25 W/kg) than 5 mW/cm^2 (0.75 W/kg), but no values of the RFR groups differed significantly from those of the sham group. The authors suggested that the decreases in seizure latency and increases in seizure intensity at 15 mW/cm^2 could have resulted from local brain hyperthermia rather than alteration of the PTZ effect on brain neuronal activity.

The results of the second experiment were unclear. Rats given 7.5 mg/kg of CDZ had longer latencies after exposure at 15 mW/cm^2 (2.25 W/kg) than at lower levels, and latencies of rats given 15 mg/kg were shorter after exposure at 5 mW/cm^2 (0.75 W/kg) than for sham exposure or exposure at 10 or 15 mW/cm^2 (1.5, or 2.25 W/kg). The authors suggested that the positive findings may be ascribable to random (Type II) statistical error. They therefore did a third experiment, the results of which did not support the earlier findings that 15 mW/cm^2 (2.25 W/kg) or even 20 mW/cm^2 (3 W/kg) enhanced PTZ seizures and increased the antiseizure protection of CDZ at 7.5 mg/kg. They therefore regarded the few apparently positive results as spurious, Type II errors, but did not rule out possible experimenter bias.

Lai et al. (1983) exposed unrestrained rats to pulsed, circularly-polarized 2.45-GHz RFR (2-μs pulses, 500 pps) in cylindrical waveguides (Guy et al., 1979) for 45 minutes at a spatially-averaged power density of 1 mW/cm^2. By calorimetry, the whole-body SAR was 0.6 W/kg. The authors noted

that at this SAR, the range of average power densities for linearly polarized RFR would be 3-6 mW/cm^2. Control rats were sham exposed. The effects of one of several drugs given right after exposure were studied.

In the first experiment, the effect of the RFR on the stereotypy induced by subcutaneous apomorphine injection was studied: Rats were scored on which of five different forms of behavior they exhibited during 5-minute observation periods right after apomorphine injection and after four 15-minute intervals. The results yielded a higher mean score for RFR-exposed rats than for sham-exposed rats and indicated that RFR exposure produced more intense stereotypy, with biting and clawing, than did sham exposure. The effect of the RFR on the hypothermia induced by apomorphine was also studied. First, colonic temperatures were measured right after RFR- or sham exposure. Then the rats were injected with apomorphine and their colonic temperatures were recorded four more times at 15-minute intervals. At 15 minutes after drug injection, the mean temperature of the RFR group had decreased by 0.95 ^{o}C, whereas the decrease was only 0.63 ^{o}C for the sham group, a significant difference showing that the hypothermic effect of apomorphine was enhanced by the RFR.

Next, the effect of the RFR on stereotypy induced by d-amphetamine was studied. Each rat was injected with the drug right after exposure and was watched for the presence of any of three normal behaviors and three abnormal behaviors. Starting 4 minutes after injection, they were observed for 1 minute every 5 minutes for an hour. The difference in average score between the RFR and sham groups for the six behaviors was nonsignificant.

Also studied was the effect of the RFR on the hyperthermia induced by d-amphetamine. Colonic temperatures of rats were measured right after exposure and at 15-minute intervals for 90 minutes after drug injection. Results were shown as the mean colonic temperature change for each group versus time interval after injection. The mean temperature at zero time was 38.3 ^{o}C for the RFR group and 38.2 ^{o}C for the sham group. The mean temperature of the sham group reached its maximum at 45 minutes, at which time it was 1.4 ^{o}C higher, and then it diminished to about 39.3 ^{o}C at the end of the 90-minute period. By contrast, the temperature of the RFR group reached its maximum at 60 minutes, an increase of 1.2 ^{o}C, and diminished to 39.2 ^{o}C at 90 minutes. These differences in time-dependent increases in temperature were significant.

In the final experiment, rats were injected with morphine at doses ranging from 1 to 20 mg/kg immediately after exposure. The number of rats that exhibited catalepsy (general muscular rigidity and a certain posture for more than 1 minute) 30 minutes after injection was recorded. Also recorded was the number of rats that died within 2 hours after injection.

The differences in the percentages of RFR-exposed and sham-exposed rats that exhibited catalepsy were reported to be significant. However, in an erratum (Lai et al., 1985), the authors indicated that the statistical method used was inappropriate. Use of another statistical method showed that the responses of the sham group increased with drug dose, but that the responses of the RFR group were not dose-dependent.

The original paper noted that no deaths had occurred in the RFR or sham group at doses of 1 or 5 mg/kg but that the differences in percentages of deaths at the larger doses were significantly higher in the RFR group. In the erratum, however, the authors noted that they found no significant differences in deaths due to the RFR.

It is interesting that the mean colonic temperatures of the apomorphine-injected and amphetamine-injected groups immediately after exposure to RFR were both 0.1 ^{o}C higher than for their respective sham-exposed groups (38.3 versus 38.2 ^{o}C in both cases). Not clear was the influence of thermoregulation on those results. Would similar results be obtained if pre-injection colonic temperatures were raised by the same amount by an agent other than RFR?

Lacking in this investigation were data on control animals given saline instead of the drugs. Such data might have more clearly delineated subtle non-RFR factors that may have influenced the results.

In a similar study, Lai et al. (1984a) examined the effects of the same RFR on the actions of pentobarbital in the rat. In the first of two series, unanesthetized, unrestrained rats were exposed to the RFR. Each rat's colonic temperature was taken right after exposure, after which the rat was injected with sodium pentobarbital at a dose sufficient to induce surgical anesthesia. After the rat lost its righting reflex, its colonic temperature was recorded at 15-minute intervals for 150 minutes, and the time interval after injection to regain the righting reflex was noted. A group of rats was sham-exposed and similarly treated.

In the second series, baseline colonic temperatures were measured and the rats were injected with pentobarbital. After 15 minutes, by which time all of the rats had lost their righting reflex, some rats were exposed to the RFR for 45 minutes anteriorly (head toward source) and other rats posteriorly (rear toward source). Their colonic temperatures were recorded for 90 minutes after exposure as were their time intervals for regaining the righting reflex.

The (conscious) rats in the first series did not show any preferred orientation during RFR exposure and there was no significant difference in mean colonic temperature between the RFR and sham groups immediately after exposure (37.8 ^{o}C for both). The mean colonic-temperature changes for each group versus time after pentobarbital injection indicated that both groups reached maximal hypothermia (about -3 ^{o}C) at 75 minutes. Mean temperature depressions of the RFR group did not differ significantly from those of the sham group at corresponding times up to 105 minutes. Between 105 to 150 minutes, the mean depressions for the RFR group were significantly larger than for the sham group, i.e., the recovery of the RFR group from the hypothermia was slower. Also, the mean time to righting-reflex recovery for the RFR group was significantly longer than for the sham group.

In the second series, the baseline mean colonic temperatures of the injected rats before RFR- or sham exposure were 37.9 ^{o}C. The mean colonic temperatures of the RFR groups right after anterior-exposure and posterior-exposure were respectively 34.6 and 34.7 ^{o}C, and was 34.1 ^{o}C for the sham group. The difference between the two RFR groups was not significant, but

both values were significantly higher than for the sham group. All three groups attained maximal hypothermia 30 minutes after exposure (45 minutes after injection). The mean changes at that time for the posterior-RFR, anterior-RFR, and sham groups were respectively about -3.8, -4.2, and -4.5 ^{o}C, but only the difference between the posterior-RFR and sham groups was significant.

From 30 to 90 minutes, all three groups showed recovery toward the baseline temperatures. However, the posterior-RFR group recovered from the hypothermia earlier and recovered their righting reflex more quickly than the anterior-RFR and sham groups. The authors surmised that those findings were due to differences in local energy deposition in the two orientations, which could yield differences in drug metabolism or kinetics.

Lai et al. (1984b) also did experiments to determined the effects of the same RFR on ethanol-induced hypothermia and ethanol consumption. For the ethanol-hypothermia experiment, 15 rats were RFR exposed and 14 were sham-exposed for 45 minutes. Immediately after exposure, each rat was removed from its waveguide, its colonic temperature was measured, and it was injected with a solution of ethanol (3 g per kg of body weight in 25% of water by volume). Afterward, the colonic temperatures of the rats were measured again at 15-minute intervals for 120 minutes.

The mean colonic temperature of the RFR-exposed rats at exposure end did not differ significantly from that of the sham-exposed rats. Ataxia developed within 5 minutes of ethanol injection, but the righting reflex remained intact. The mean colonic-temperature changes versus time after ethanol injection for the two groups showed that hypothermia had occurred in the RFR group at a significantly slower rate than in the sham group, but the temperature depressions of both groups became about the same 90 minutes after injection.

In the ethanol-consumption study, rats were given 90-minute sessions in the waveguides daily for 9 days. On the first three days, the rats were inserted in the waveguides for 45 minutes with the RFR source on "standby". At this time, a bottle containing a 10% sucrose solution was inserted in each waveguide and the amount consumed during the remaining 45 minutes was measured. On the fourth day, the procedure was the same but half the rats (24) were exposed to the RFR for the full 90 minutes, and the other half were sham exposed. On the next three days, the procedure was the same, but a solution of 15% ethanol + 10% sucrose was used (the latter to render the ethanol more palatable). On the eighth day, half the rats were exposed to the RFR for 90 minutes, the remaining were similarly sham exposed, and the amounts of sucrose-ethanol solution consumed were measured. On the ninth day, the roles of the two groups were reversed: the first group was sham exposed, and the second was RFR exposed. The results indicated that the RFR had no apparent effect on sucrose consumption, but that it increased the consumption of the sucrose + ethanol solution.

It should be noted that there were significant differences in mean baseline temperatures among the groups given different dosages, and that there was an apparent discrepancy in mean baseline temperatures between the sham-saline groups. Such differences among control groups, as well as the

significant colonic-temperature rises during both RFR- and sham exposure, indicate the presence of large uncontrolled factors and render questionable most of the findings of this study.

Lai et al. (1992) exposed rats to the same pulsed RFR (2-μs pulses of 2.45-GHz RFR at 500 pps) at a whole-body SAR of 0.6 W/kg either once for 45 minutes or for 10 daily 45-minute sessions to determine the effects of the RFR on the concentration and affinity of benzodiazepine receptors in the cerebral cortex, hippocampus, and cerebellum. The results of the single exposures indicated a significant increase of receptor concentration in the cerebral cortex but not in the hippocampus or cerebellum. There were no significant changes in the binding affinity of the receptors in any of the three regions. The results for the multiple exposures showed no change in receptor concentration right after the last exposure, a possible indication of adaptation to repeated exposures.

In a separate experiment, rats adapted first to the experimental situation and then exposed once to the RFR showed significantly higher benzodiazepine-receptor concentrations in the cerebral cortex than did similarly treated sham-exposed rats. Those results led the authors to suggest that because such receptors are responsive to anxiety and stress, low-level RFR can be a source of stress.

In overall summary, the studies on possible synergism between RFR and psychoactive drugs such as diazepam, chlorpromazine, chlordiazepoxide, and dextroamphetamine, yielded unclear or inconsistent results. In some studies, the changes in drug dose-response relationship were subtle and not necessarily induced by the RFR. In most of the studies that yielded RFR-induced changes in drug response, whole-body SARs of 0.6 W/kg or average power densities of 1 mW/cm^2 or higher coupled with relatively high drug dosages were necessary. In still other studies, the results were negative (no effects). At relatively low RFR levels, the role of thermoregulation in the results is unclear and the occurrence of relatively high local SARs in the brain cannot be ruled out. Noteworthy were the negative findings of synergistic effects between alcohol consumption and exposure to RFR except at relatively high doses of alcohol.

3.8 CELLULAR AND SUBCELLULAR EFFECTS

Various studies on cellular and subcellular effects of RFR have been discussed in previous sections under other specific topics such as the blood-brain barrier, immunology, and hematology. In the present section, therefore, representative studies of other RFR effects on cells and their constituents are described.

3.8.1 STRUCTURES AND CONSTITUENTS OF MICROORGANISMS AND OTHER SINGLE-CELL SYSTEMS

Webb and Dodds (1968) sought effects of RFR at frequencies above 30 GHz (millimeter waves) on the growth of E. coli bacteria. The results appeared to indicate that bacterial growth was inhibited by 136-GHz RFR. No statistical treatment was given, but examination of the data indicated the likelihood that non-RFR factors were present. Webb and Booth (1969) also reported RFR absorption by E. coli cells, and by preparations of E. coli

protein, RNA, and DNA at specific (resonant) frequencies in the range 65-75 GHz. The latter findings were difficult to evaluate because of absence of adequate information on methodology, instrumentation, and statistical treatment.

Several studies sought to confirm predictions by Fröhlich (1975) of resonances above 30 GHz. In one study, Webb and Stoneham (1977) reported the detection of resonances in the range 70-5000 GHz in active cells of E. coli and B. megaterium, using laser Raman spectroscopy. They found no resonances in resting cells, cell homogenates, or nutrient solutions, and therefore associated those for active cells with metabolic processes.

Cooper and Amer (1983) disputed the findings above, indicating that cell suspensions yield spurious Raman lines in the frequency range of interest under certain conditions, notably by Mie scattering from cell clumps, and that they thereby were able to reproduce many of the spectra.

Gandhi et al. (1980) used a stable, computer-controlled system to measure RFR absorption in various biological specimens at frequencies in the range 26.5-90.0 GHz in small steps. They studied solutions of DNA from salmon sperm and RNA from whole yeast and yeast-like fungi, and suspensions of E. coli cells and baby-hamster-kidney cells transformed with mouse sarcoma virus. Those results showed no resonances at any frequency sampled, strongly suggesting that none of those biological materials absorb significant RFR energy in that range.

Swicord and Davis (1983) used a new method for measuring absorption by optically transparent liquids and for studying interactions between cellular constituents and RFR at frequencies below (as well as above) the millimeter range. They measured RFR absorption in the range 8-12 GHz by aqueous solutions of DNA extracted from E. coli. A plot of attenuation coefficient for DNA versus frequency exhibited no resonances, but the attenuation increased linearly with frequency and its values were much higher than for physiologic (Ringer's) solution or deionized water at the same frequencies.

Edwards et al. (1985) noted that biochemical analysis of the DNA solution used in the previous study showed the presence of significant amounts of RNA and protein impurities, and that the DNA had been sheared extensively by improper handling. In addition, the enhanced absorption observed for such samples in the range 8-12 GHz was absent for carefully prepared DNA samples of high molecular weight that were free of protein and RNA.

Gabriel et al. (1987) described the efforts in London and Uppsala by two independent laboratories to detect resonances in the range 1-10 GHz for aqueous solutions of circular DNA molecules of the same form studied by Edwards et al. (1985). The dielectric measurements in London were done on an automated time domain spectrometer using a reflection technique; those in Uppsala were done with a similar spectrometer, but with a transmission technique. The authors noted that a common and most important feature of such measurements is the use of a reference sample to normalize reflection or transmission coefficients, thus eliminating systematic experimental artifacts, such as slight impedance mismatches.

Plots of relative permittivity and loss factor of a 0.1% plasmid DNA solution at 20 ^{o}C versus frequency obtained in London were displayed on linear scales, to permit direct comparison with those of Edwards et al. (1985). Those from Uppsala were shown as the more common log-log plots. Each point was the average of up to 36 measurements on samples from four plasmid preparations; no variances were shown, but the authors estimated the measurement uncertainties to be about 1% for permittivity and 2% for loss factor. Also shown on each plot were lines of relative permittivity and loss factor for pure water. Within those limits, the measured values of permittivity and loss factor for DNA were all close to those for pure water.

The values of attenuation coefficient and incremental attenuation coefficient relative to water were plotted versus frequency; displayed also were those of Edwards et al. (1985). Unlike the results for the latter, no resonances were evident; the incremental attenuation values were scattered above and below the zero line, with the largest deviations less than ±0.1 per cm, primarily in the upper 20% of the frequency range. By contrast, the incremental attenuation values by Edwards et al. (1985) at their reported resonant frequencies ranged from 0.28 to 0.7 per cm.

Foster et al. (1987), in another endeavor to reproduce the findings of Edwards et al. (1985), used two techniques. In one technique, which was a variant of that used by Edwards et al. (1985), a probe consisting of the open end of a length of coaxial line was immersed in the sample and the complex reflection coefficient at its tip was measured with an automatic network analyzer (ANA) in the frequency range 0.045-18 GHz in 0.045-GHz increments. The authors surmised that the previously reported apparent resonances could be ascribed to two sources of error associated with such probe measurements. First, the coaxial connector to the probe could be a source of artifactual reflection. Accordingly, they did the measurements with and without use of a time-domain-gating procedure for removing connector artifact. Second, analyses of the measurements did not account for radiation from the probes used by Edwards et al. (1985) and themselves. In the other technique, the sample was placed inside a section of 7-mm coaxial transmission line between a Teflon disk and a short circuit terminating the line, thus avoiding probe radiation, and the reflection coefficient from the sample was measured with an ANA.

With the probe method and no time-domain gating to remove connector artifact, solutions of DNA having about threefold higher concentration than those used by Edwards et al. (1985) yielded reflection-coefficient oscillations crudely resembling the resonances reported by the latter; however, those oscillations were eliminated by the time-domain gating. No apparent resonances were seen with the transmission-line technique.

Sagripanti et al. (1987) reported that plasmid DNA (derived from E. coli and purified to ensure the absence of protein contaminents), when exposed to low-levels of RFR in the frequency range 2.00 to 8.75 GHz, exhibited both single-strand and double-strand breaks, but only if small amounts of copper ions (cuprous but not cupric) were present. Samples consisted of 10 μg of plasmid DNA in 28 μl of buffer, with each sample contained within a 1.5-ml micro test tube.

Exposures were done by immersing an open-ended coaxial probe into each sample. The probe consisted of a solid outer conductor 3.58 mm in diameter and a central conductor 1 mm in diameter, both of copper, with solid dielectric between them and with a flush open end. Measurements of attenuation and standing-wave ratio were done with a dual-directional coupler and a slotted line inserted between a generator of CW RFR and the probe. The results were used to determine the maximum and minimum SARs (SAR_{max} and SAR_{min}). Those data indicated that SAR_{max} was about five times larger than SAR_{min}, with SAR_{true} somewhere between the two. The experimental results were referenced to the values of SAR_{max}.

In the first experiments, samples were sham-exposed or exposed for 20 minutes to 2.55-GHz RFR at an SAR_{max} of 10 W/kg. The results of six experiments showed that the mean number of double-strand breaks in the RFR-exposed samples was significantly higher than for the sham-exposed samples. The authors regarded such exposures as nonthermal, because of the large surface-to-volume ratio of the samples and thus their ability to dissipate heat readily; the authors indicated that exposures at levels of about 1 kW/kg were needed to detect any significant temperature rises in the samples.

In other experiments toward seeking frequency specificity of the effect, samples were exposed to RFR at 8.75 GHz, which, with 2.55 GHz, were previously found frequencies of maximum resonant absorption by DNA, and to 2.00-GHz, 3.45-GHz, and 7.64-GHz RFR, which were frequencies of minimum absorption (Edwards et al., 1985). The authors stated that they could not find any variation in double-strand breaks attributable to resonant absorption by DNA.

For statistical analysis, the authors pooled data on 12 experiments at the five frequencies above. The results showed a significantly higher mean percentage of double-strand breaks for the RFR-exposed samples than the sham-exposed samples. However, the mean percentage of double-strand breaks for the sham-exposed samples was also significantly higher than for control samples, for which the copper probe was close to the sample but not in contact with it. When the probe was covered with a thin plastic coating, the difference between sham-exposed and control samples vanished, but also no strand breaks were detected in RFR-exposed samples.

In other experiments, samples were incubated in either cupric or cuprous chloride, or in the storage buffer (controls), and not RFR- or sham-exposed. The results indicated that only incubation in cuprous chloride mimicked the strand breaking seen with RFR exposure. Based on linear increases of damage with exposure duration, the authors concluded that the presence of cuprous chloride (in the probe) causes the strand breaking and that the RFR increases the effect.

3.8.2 SUMMARY

Webb and Dodds (1968) sought effects of RFR at specific frequencies above 30 GHz (in the millimeter-wave region) on growth of E. coli bacteria. The results appeared to show that bacterial growth was inhibited by 136-GHz RFR, but from examination of the data, the presence of non-RFR factors was likely. Webb and Booth (1969) also reported absorption of RFR by E. coli

cells, and by preparations of protein, RNA, and DNA derived from E. coli at specific (resonant) frequencies within the range 65-75 GHz. The latter findings were difficult to evaluate because no adequate information on methodology, instrumentation, and statistical treatment was given.

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Swicord and Davis (1983) used a new method for measuring absorption by optically transparent liquids and for studying the interactions between cellular constituents and RFR at frequencies below (as well as above) the millimeter range. They measured RFR absorption in the range 8-12 GHz by aqueous solutions of DNA extracted from E. coli. A plot of attenuation coefficient for DNA versus frequency exhibited no resonances, but the attenuation increased linearly with frequency and its values were much higher than for physiologic (Ringer's) solution or deionized water at the same frequencies. Edwards et al. (1985) noted that biochemical analysis of the DNA solution used in the Swicord and Davis (1983) study indicated the presence of significant amounts of RNA and protein impurities, and that the DNA had been sheared extensively by improper handling. In addition, the enhanced absorption observed for such samples in the range 8-12 GHz was absent for carefully prepared DNA samples of high molecular weight that were free of protein and RNA.

Gabriel et al. (1987) described the efforts in two laboratories (London and Uppsala), respectively using a reflection technique and a transmission technique, to detect resonances in the range 1-10 GHz for aqueous solutions of circular DNA molecules of the form studied by Edwards et al. (1985). The authors noted that a most important feature of both of their techniques is use of a reference sample to normalize reflection or transmission coefficients to eliminate systematic experimental artifacts, such as slight impedance mismatches. Plots of relative permittivity and loss factor of a plasmid DNA solution versus frequency yielded values close to those for pure water, and similar plots of attenuation coefficient and incremental attenuation coefficient relative to water did not show any of the resonances reported by Edwards et al. (1985).

Foster et al. (1987) also tried to reproduce the findings of Edwards et al. (1985). They thought that the apparent resonances might be due to reflection artifact from the coaxial connector to the probe used for the measurements and to lack of consideration of possible radiation from the probe. Accordingly, they did the measurements with and without use of a time-domain-gating procedure for removing connector artifact. Without using time-domain gating to remove connector artifact, Foster et al. (1987) obtained reflection-coefficient oscillations crudely resembling resonances reported by Edwards et al. (1985) in solutions of DNA having a threefold higher concentration than used by the latter. Those oscillations were eliminated by time-domain gating. In addition, Foster et al. (1987) used another measurement technique that eliminated probe radiation, and saw no resonances.

Sagripanti et al. (1987) reported that plasmid DNA, when exposed to low-levels of RFR in the frequency range 2.00 to 8.75 GHz, exhibited both single-strand and double-strand breaks, but only if small amounts of copper ions (cuprous but not cupric) were present. Samples consisted of 10 μg of plasmid DNA in 28 μl of buffer within a 1.5-ml micro test tube. A coaxial probe, with both inner and outer conductors of copper, was immersed into each sample for exposure. Measurements of attenuation and standing-wave ratio were used to determine the maximum and minimum SARs (SAR_{max} and SAR_{min}). Those data indicated that SAR_{max} was about five times larger than SAR_{min}, with SAR_{true} somewhere between the two. The experimental results were referenced to the values of SAR_{max}.

First, samples were sham-exposed or exposed for 20 minutes to 2.55-GHz RFR at an SAR_{max} of 10 W/kg. The results showed that the mean number of double-strand breaks in the RFR-exposed samples was significantly higher than in the sham-exposed samples. The authors regarded such exposures as nonthermal, because of the large surface-to-volume ratio of the samples and thus their ability to dissipate heat readily. They noted that exposures at levels of about 1 kW/kg were needed to detect any significant temperature rises in the samples.

Next, in experiments toward seeking frequency specificity of the effect, samples were exposed to RFR at 8.75 GHz, which, with 2.55 GHz, were previously found by Edwards et al. (1985) to be frequencies of maximum resonant absorption by DNA. They also exposed samples to 2.00-GHz, 3.45-GHz, and 7.64-GHz RFR, which were frequencies of minimum absorption reported by those authors. The results showed no variations in double-strand breaks attributable to resonant absorption by DNA.

For statistical analysis, the authors pooled data on 12 experiments at the five frequencies above. The results showed a significantly higher mean percentage of double-strand breaks for the RFR-exposed samples than the sham-exposed samples. However, the mean percentage of double-strand breaks for the sham-exposed samples was also significantly higher than for control samples, for which the copper probe was close to the sample but not in contact with it. When the probe was covered with a thin plastic coating, the difference between sham-exposed and control samples vanished, but also no strand breaks were detected in RFR-exposed samples.

In other experiments, samples were incubated in either cupric or cuprous chloride, or in the storage buffer (controls), and not RFR- or sham-exposed. The results indicated that only incubation in cuprous chloride mimicked the strand breaking seen with RFR exposure. Based on linear increases of damage with exposure duration, the authors concluded that the presence of cuprous chloride (in the probe) causes strand breaking and that the RFR increases the effect.

In overall summary, many of the early studies on microorganisms produced results that were taken as evidence of nonthermal effects of RFR. The existence of resonances at frequencies above 30 GHz was postulated on theoretical grounds, and several studies were done that appeared to confirm that hypothesis. However, later studies with the use of more sophisticated engineering and biological techniques and in which artifacts were reduced significantly, yielded results that did not confirm earlier findings of resonances or other evidence of nonthermal effects at such frequencies.

The apparent absorption resonances in the range 2-9 GHz reported for aqueous solutions of DNA molecules derived from E. coli were regarded as indicative of direct action of RFR with such molecules. Later attempts endeavors to reproduce such findings, however, yielded negative results. In addition, analytical and experimental results were obtained indicating that such resonances were most likely artifactual, associated with the probes and measurement methodology used.

3.8.3 CONCLUSIONS

In general, research on possible RFR effects on microorganisms or of RFR exposure *in vitro* of cell preparations derived from macroorganisms is important toward eliciting possible mechanisms of direct interaction of RFR with such biological entities or their constituents at levels that can be characterized as nonthermal. However, the relevance of such findings to possible effects of exposure of intact animals to RFR and ultimately the significance of such findings with regard to possible hazards of RFR to humans would have to be established.

4. UNRESOLVED ISSUES

The potential biological effects of RFR at frequencies up to 300 GHz have been assessed from representative peer-reviewed studies published in the scientific literature. The preponderance of evidence indicates that chronic exposure of the public to the RFR levels generally prevailing in the environment is not hazardous to human health. Nevertheless, there are several basic uncertainties, summarized below, regarding biological effects of RFR.

(1) Many of the epidemiologic studies on possible bioeffects of RFR were extensive and well done, but contained defects or uncertainties in varying degrees, such as imprecise assignment of individuals to exposure and control groups; difficulties in obtaining accurate medical records, death certificates, or responses to health questionnaires for individuals included in both the exposure and control groups; and most important, the large uncertainties about the frequencies, levels, and exposure durations for those

selected for inclusion in exposure groups and the amount of exposure received by those selected for inclusion in control groups.

(2) As noted in Section 1.2, applying results on laboratory animals to humans, though essential, is an expedient that contains fundamental problems and uncertainties due to the basic differences between humans and other species. Investigations with nonhuman primates may narrow some of the interspecies gaps considerably, but at costs that are often prohibitive. Thus, major reductions in such uncertainties seem unlikely in the near future.

(3) The results of many investigations indicate the existence of threshold RFR levels for various bioeffects, thus providing confidence that exposure to levels that are appreciably below the thresholds are most unlikely to be deleterious. However, most experimental data that indicate the existence of thresholds were obtained by use of single or repetitive exposures of relatively short durations. Although it is hard to conceive of mechanisms whereby RFR exposures at well below threshold values over a long time are cumulative, very few investigations have been done that involve essentially continuous exposure of animals to low-level RFR (below threshold levels or those that can cause significant heating) during most of their lifetimes. The high costs of such chronic studies and the low probability that any positive effects will be found are major reasons why such studies are not given high priority by funding agencies.

(4) Regarding the basic mechanisms of interaction between RFR and various biological entities, many important discoveries have been made recently, notably by exposure of cells and subcellular structures and constituents *in vitro* to relatively low levels of RFR. The effects on such entities can be characterized as nonthermal, but the gap between such effects and possibly hazardous effects on intact humans or animals from exposure to such RFR levels is enormous. Factors such as large body masses, penetration depth and internal field distributions, and changes in body orientation during exposures to RFR *in vivo* can vastly moderate such interactions or remove them entirely. Moreover, the life processes per se are extremely complex. For these reasons, this gap is not likely to be reduced to any great extent.

5. MISCONCEPTIONS

As noted in Section 2.1, popular media often do not distinguish between RFR (nonionizing radiation) and ionizing radiation, so concern is frequently raised in the general public, with no scientific basis, that RFR can give rise to hazardous effects known to be caused by ionizing radiation. In essence, any quantum of ionizing radiation absorbed by a molecule yields up enough energy to expel an electron from the molecule (ionize it), leaving it positively charged and thus strongly enhancing the interactions of the molecule with its neighbors. Such interactions can alter the functions of biological molecules fundamentally and irreversibly in living organisms.

By contrast, the energy in a quantum of RFR is so much smaller than in a quantum of ionizing radiation that the primary effect of RFR quanta is to agitate molecules rather than ionize them. The absorption of RFR quanta at high rates (in large numbers per unit time) is necessary to produce

physiologically significant heat. Moreover, such RFR molecular agitation begins to diminish immediately on cessation of exposure.

It is also necessary to distinguish between an effect and a hazard. For example, a person's metabolism can be increased harmlessly by mild exercise. Analogously, an effect produced at RFR intensities that yield heat that can be easily accommodated within the thermoregulatory capabilities of an individual may not necessarily be deleterious. Also, any effects produced thereby are generally reversible. However, the thermoregulatory capabilities of any given species may be exceeded at high RFR intensities, so compensation for such effects may be inadequate. Thus, exposure at such intensities can cause thermal distress or even irreversible thermal damage.

As noted in Section 2.1, it is not scientifically possible to guarantee that exposure to RFR (or any other agent) that does not cause deleterious effects for relatively short exposures at low levels will result in the appearance of deleterious effects many years in the future. As noted above, however, the large body of experimental data indicate the existence of threshold levels for various RFR bioeffects and that low-level exposures are not cumulative.

6. GENERAL CONCLUSIONS

6.1 ACTUAL OR PRESUMED EXPOSURE OF HUMANS

Considerable weight should be given to findings of well performed studies involving actual or presumed human exposure to RFR despite the limitations of such studies, because of the problems and uncertainties in animal studies related to interspecies differences. Analyses of the findings of various epidemiologic studies on the effects of RFR exposure, either occupationally or from residing in the vicinity of RFR emitters, and those of studies with human volunteers, produced no unequivocal evidence that chronic exposure to RFR at levels within the ANSI 1982 exposure guidelines or the 1991 SCC-28 exposure guidelines was implicated in reported detrimental health effects.

Individual cases of eye damage from occupational exposure to RFR have been reported at various times since the end of World War II; some of those cases may have been caused by exposure to RFR at substantially higher levels than the threshold found in studies with animals (about 150 mW/cm^2). Also, several epidemiologic studies were performed to determine whether ocular damage could be statistically associated with occupational exposure to RFR. Most of the positive findings in humans were found to be due more to aging than RFR exposure. Some exceptions were cases of possible occupational exposure of individuals at levels and durations likely to have been sufficient to heat the eye to temperatures well in excess of those found damaging in animal experiments.

The possible association of congenital abnormalities with prenatal exposure to RFR has been reported. Careful analyses of such reports do not substantiate such findings.

6.2 STUDIES WITH ANIMALS

RFR-induced teratogenesis was sought in various species of insects, birds, rodents, and nonhuman primates. In early studies with insects, notably the darkling beetle, the RFR levels used were usually high enough to significantly heat the subjects. Nevertheless, those investigators had concluded that the terata they found were not due entirely to the heat produced by the RFR. Subsequent investigators, however, were unable to confirm such nonthermal findings, and they suggested that the earlier findings could be ascribed to uncontrolled non-RFR factors. Thus, there is no valid scientific evidence for the occurrence of teratogenic effects in the darkling beetle at nonthermogenic RFR levels.

A similar conclusion applies to studies of RFR-induced teratogenesis in quail eggs and developmental abnormalities in hatched quail. On the other hand, retardation of development in embryos of the domestic chicken was ascribed by others to exposure of eggs to RFR at relatively low RFR levels (about 3.5 mW/cm^2 average). In the chicken studies, the ambient temperatures were selected to compensate for the RFR-induced rises in the mean internal temperature of the eggs. However, other investigators showed that the local spatial temperature variations within RFR-exposed eggs are much higher than in sham-exposed eggs. Thus, even though the spatially averaged temperatures of the RFR- and sham-exposed eggs were rendered about the same, the temperatures at various internal locations in the RFR-exposed eggs most likely significantly exceeded the highest local temperatures within the sham-exposed eggs. Therefore, the reported nonthermal RFR teratogenesis in the chicken is questionable.

Mixed results were obtained in studies of RFR-induced teratogenesis and developmental abnormalities in rodents. With mice, both positive and negative findings were reported, but several of the more recent studies reported statistically significant retardation in postnatal growth from RFR exposure *in utero* at levels exceeding 10 mW/cm^2 (an effect found with hamsters as well). On the other hand, virtually all of the studies with rats yielded negative results and indications that the RFR levels that can cause significant prenatal terata or retardation of postnatal growth or development are close to, or above, the lethal level for rat dams.

The findings above with rats and mice led one group of researchers to conclude that the mouse may be more suitable than the rat as a model for investigations of possible teratogenic effects of RFR in humans. However, the positive findings in one rodent species and the negative findings in another rodent species suggests that neither rodent species is a suitable model for that purpose. Instead, investigations with nonhuman primates should yield much more definitive findings.

In a study primarily seeking effects of RFR exposure on mother-infant behavior in squirrel monkeys, a small number of unexpected infant deaths occurred in the RFR-exposure groups (at whole-body SARs up to 3.4 W/kg). The number of deaths in the control groups was still smaller, so the results showed borderline statistical significance. However, in a followup study specifically directed toward possible RFR-induced infant mortality, which involved a larger number of monkeys, no statistically significant difference in numbers of infant deaths between RFR-exposed and control groups was seen.

Overall, the studies performed on possible RFR-induced teratogenesis and developmental abnormalities support the conclusion that such effects can occur from temperature increases caused by the RFR rather than from any special teratogenic properties of RFR. However, those findings also indicate that it is most unlikely that such effects would occur in humans from exposure to nonthermal levels of RFR.

In many studies of possible mutagenic effects of RFR on bacteria, yeasts, or fruit flies, the findings indicated that mutations do not occur except under conditions in which the RFR produces significant temperature rises in the specimens. Regarding mutagenesis in mammals, several studies showed that exposure of male rodents to levels of RFR that produce frank heating of the testes tends to reduce fertility, but that such levels were not mutagenic. No scientifically valid evidence was found that chronic exposure to RFR at levels within the 1982 ANSI or 1991 SCC-28 standards induces or promotes any form of cancer in mammals. This conclusion also applies to the University of Washington chronic study with rats, summarized later.

Regarding possible effects of RFR on the nervous system, many early studies of the blood-brain barrier (BBB) are believed to have suffered from the presence of significant artifact in the biological methodology used. In other studies, the results interpreted by the investigators as RFR-induced alterations of the BBB were more likely ascribable instead to changes in the relative sizes of vascular and extravascular volumes in the brain. In recent studies, however, in which artifact was reduced substantially and perhaps rendered negligible, the results indicate that hyperthermic levels of RFR are necessary to alter the BBB.

Most of the positive findings of histopathological and histochemical changes in the nervous system by RFR were probably induced thermally. A notable exception was a recent study, which indicated that inhibition of the biochemical respiratory chain function within certain cells can be induced at RFR levels that do not cause measurable tissue hyperthermia. That effect is worthy of further study, but is not indicative of any potential health hazard.

Problems associated with the use of metallic electrodes to record EEGs and evoked responses during RFR exposure led to discounting of the positive findings in studies involving such use. Such problems were essentially eliminated by development of high-resistance, carbon-loaded-Teflon electrodes that were tissue-compatible and thus implantable for chronic studies. When such electrodes were used to measure EEGs and/or evoked responses of conscious (unanesthetized) animals during exposure, the differences between responses of RFR-exposed and sham-exposed animals were nonsignificant. It is noteworthy that for rabbits, used frequently for such studies, the EEGs and evoked responses were found to vary widely among unanesthetized control animals, as well as with time in individual rabbits, thereby reducing the confidence in any positive or negative findings with rabbits.

Possible RFR effects on the immune system were sought in a variety of investigations. In many early studies, suspensions of the various classes of white blood cells (leukocytes) were exposed to RFR *in vitro*, but such studies suffered from the lack of adequate control of cell temperature during

exposure. In later studies, therefore, considerable effort was devoted to the development of exposure systems that permitted maintenance of cell temperature constant at optimum level during exposure or that provided means for deliberate temperature increases to specified values for comparison. Many studies with such systems were directed toward determining the effects of RFR on lymphocyte proliferation (without and with stimulation by various mitogens) or on functional characteristics of lymphocytes as components of the immune system.

In studies of leukocyte cultures in which were held at the same temperature during RFR exposure as control cultures, negative findings (nonsignificant differences between exposed and control cultures) were obtained. In those that yielded positive findings, the effects on the exposed cultures were clearly thermal.

Also sought in early studies were possible effects of exposure of red blood cells (erythrocytes) to RFR *in vitro*. Among the findings were significant cell breakdown (hemolysis) and potassium-ion (K^+) efflux for rabbit erythrocytes exposed to 2.45-GHz RFR at average power densities as low as 1 mW/cm^2. In later studies, however, hemoglobin and K^+ losses from rabbit erythrocytes by heating with RFR from room temperature to 37 ^oC did not significantly differ from losses due to conventional heating; the threshold SAR for effect was found to exceed 46 W/kg. Significant hemolysis and K^+ loss were not found for human erythrocytes heated by either means to 37 ^oC, thus indicating that RFR may not induce similar changes in rabbit and human blood.

Exposure of animals to RFR *in vivo* for determining possible effects on the immune system yielded mixed results. Some of the studies showed an apparent diminution of immune responses to RFR, but with no clear dependence on RFR level. Results of other studies appeared to indicate that survival was extended by exposure to RFR. In investigations with Japanese quail, RFR-related differences in antigenic responses were not found, except when temperature elevations were implicated. Some of the investigators reported that exposure of mammals to RFR increased the proliferation of leukocytes or the production of antibodies (relative to controls), but with few exceptions, measured or estimated SARs were well in excess of 1 W/kg. In more recent studies, subtle effects on mammalian immune systems were sought, using advances in assay methods. Sought in some investigations were effects of RFR on the activity of natural killer (NK) cells, with attention to possible effects of non-RFR stress. The results indicated that SARs well in excess of 1 W/kg were necessary for such effects.

More directly relevant to possible effects of RFR exposure on the human immune system would be studies in which animals are exposed to RFR continuously for long periods, to determine whether such exposure would adversely affect their health, longevity, and resistance to natural disease or experimental challenge with various microorganisms or toxins therefrom. Because of limitations in funding, however, relatively few such studies have been done and even fewer have been repeated by other laboratories.

The most comprehensive chronic study to date was the University of Washington rat study mentioned above. In that study, 100 rats had been exposed to 2.45-GHz RFR and 100 rats had been concurrently sham-exposed for

virtually their full lifetimes (except those withdrawn for interim tests and those that died before the end of the exposure regimen). Tests of 10 rats withdrawn from each group after 13 months of exposure (interim kill) yielded significantly higher splenic T- and B-lymphocyte counts in the RFR subgroup than in the sham subgroup; the authors ascribed those higher counts to stimulation of the lymphoid system by the RFR. This effect, however, was not seen in similar tests conducted on completion of the exposure regimen, and the authors provisionally ascribed its absence to immunosenescence. The RFR did not affect longevity at corresponding times during the regimen.

No primary malignancies were found at the interim kill (in rats younger than one year). Primary malignant lesions were found in 2 RFR-exposed and 2 sham-exposed rats at ages 13-18 months, in 9 of the RFR group and 1 of the sham group at ages 19-24 months, and in 7 of the RFR group and 2 of the sham group at ages 26-30 months. The differences in the numbers for each specific malignancy type were all statistically nonsignificant, and the incidence of each specific malignancy in the RFR group was similar to that in the literature for untreated rats of the same strain. The authors therefore concluded that those findings were not related to the RFR.

Others noted that there were totals of 18 rats with malignancies in the RFR group and 5 rats in the sham group, a statistically significant difference. (In those totals, the age differences were disregarded.) The University of Washington investigators gave little credence to this point because of the nonsignificant differences for each malignancy type and noting that combining those nonsignificant differences to attain statistical significance was an oncologically dubious procedure. They also remarked that the occurrence of benign neoplasms has considerable significance under the assumption that the initiation process is similar for both benign and malignant tumors, and they pointed to their finding that the RFR and sham groups showed no difference in the incidence of benign tumors.

Regarding other possible physiological and biochemical effects of RFR, various investigations have shown that the thermoregulatory systems of nonhuman primates can readily compensate for high levels of RFR, a finding that is most significant relative to possible hazards of human exposure because of the closer anatomical and physiological similarities among human and nonhuman primates than between those of humans and any other mammals.

Most of the studies of possible RFR-induced effects on the endocrine system were conducted on rodents. Those that yielded positive findings indicated that the effects were largely due to increases in the thermal burdens of the animals. In many of the studies, the observed changes in endocrine function may have been influenced significantly by stresses in the animals. For this reason, the studies in one laboratory are notable for the efforts taken toward reducing stress by acclimating the animals to handling and to the experimental situation. Nevertheless, some of the subtle effects of RFR on the endocrine system deserve further study.

Regarding effects of RFR on the heart, some early studies were done in which excised hearts were exposed to RFR, and other studies were done in which the whole animal was exposed *in vivo*. The positive findings reported in most of those studies (bradycardia, tachycardia, or both) were suspect because of

the use of attached or indwelling electrodes that probably introduced significant artifact. Subsequent studies involving the use of electrodes that were not perturbed by, or did not perturb, the RFR yielded results indicating that heart rates were altered only at RFR levels that caused significant body-temperature rises or otherwise added to the thermal burden of the animal.

Also investigated, both in excised animal hearts and *in vivo*, was the possibility that pulsed RFR at repetition rates that are synchronous with various periodic characteristics of the EKG could alter heart rate. In one study, tachycardia was reported to have been induced in excised frog hearts by RFR pulses in synchrony with the EKG, but this finding could not be confirmed by other researchers.

Other investigators showed that for CW RFR, levels well in excess of 1 mW/cm^2 or 1 W/kg were necessary for significant alterations of heart rate. The results of another study indicated that the functioning of hearts already damaged from other causes is not affected by exposure to CW RFR at levels of 10 mW/cm^2 or lower.

Many studies of avoidance behavior in animals appeared to indicate that RFR is a noxious or unpleasant stimulus. There is considerable evidence, however, that the RFR-induced changes in behavioral patterns observed in animals are the responses by their thermoregulatory systems, to minimize absorption of heat in normal or warm ambient environments (including high levels of humidity) or to obtain warmth in relatively cold environments. Thus, other than auditory perception of RFR pulses, animals apparently do not directly sense RFR (other than as heat). The results of studies on RFR disruption of animal performance or learned behavior were quite variable; however, most of the findings showed that the observed changes in behavior could be ascribed to the additional thermal burden imposed by the RFR, and specifically were significant at measured or estimated whole-body SARs well in excess of 1 W/kg.

The relatively few studies of possible synergism between RFR and various psychoactive drugs (diazepam, chlorpromazine, chlordiazepoxide, and dextroamphetamine) yielded unclear or inconsistent results. In some studies, the changes in drug dose-response relationship were subtle and not necessarily induced by the RFR. In most studies that yielded RFR-induced changes in drug response, average power densities of 1 mW/cm^2 or higher coupled with relatively high drug dosages were necessary. The results of still other studies showed no RFR-induced response changes. The absence of synergistic effects between the consumption of alcohol and RFR except at very high doses of alcohol were especially noteworthy.

Excitation of resonances in cells exposed to submillimeter-wave RFR was postulated on theoretical grounds, and several studies were performed that apparently confirmed that hypothesis. Specifically, preparations of E. coli and of protein, RNA, and DNA isolated from such cells yielded apparent resonances in the range 65-75 GHz, results regarded as evidence of nonthermal RFR effects. However, results of later studies, in which more sophisticated engineering and biological techniques were used to reduce artifact, did not confirm the existence of such resonances or any other indications of nonthermal effects.

Apparent resonances in the range 2-9 GHz were reported recently for aqueous solutions of DNA from E. coli, but in studies by other groups, true resonances were not found. Instead again, use of better analytical and experimental methods produced results indicating that the apparent resonances were most likely artifactual and were associated with the methodology used in the earlier studies.

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